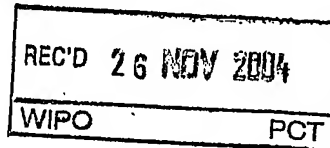




Europäisches  
Patentamt

European  
Patent Office

Office européen  
des brevets



Bescheinigung

Certificate

Attestation

Die angehefteten Unterla-  
gen stimmen mit der  
ursprünglich eingereichten  
Fassung der auf dem näch-  
sten Blatt bezeichneten  
europäischen Patentanmel-  
dung überein.

The attached documents  
are exact copies of the  
European patent application  
described on the following  
page, as originally filed.

Les documents fixés à  
cette attestation sont  
conformes à la version  
initialement déposée de  
la demande de brevet  
européen spécifiée à la  
page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

03019642.2

**PRIORITY  
DOCUMENT**  
SUBMITTED OR TRANSMITTED IN  
COMPLIANCE WITH RULE 17.1(a) OR (b)

Der Präsident des Europäischen Patentamts;  
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets  
p.o.

R C van Dijk

BEST AVAILABLE COPY



Anmeldung Nr:  
Application no.: 03019642.2  
Demande no:

Anmeldetag:  
Date of filing: 05.09.03  
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

CELLZOME AG  
Meyerhofstrasse 1  
69117 Heidelberg  
ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:  
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.  
If no title is shown please refer to the description.  
Si aucun titre n'est indiqué se référer à la description.)

Protein complexes of the Beta-amyloid precursor protein (APP) processing pathway

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s)  
revendiquée(s)  
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/  
Classification internationale des brevets:

C07K/

Am Anmeldetag benannte Vertragsstaaten/Contracting states designated at date of  
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL  
PT RO SE SI SK TR LI

## **PROTEIN COMPLEXES OF THE BETA-AMYLOID PRECURSOR PROTEIN (APP) PROCESSING PATHWAY**

### **1. FIELD OF THE INVENTION**

The present invention relates to protein complexes of the beta-amyloid precursor protein (APP) processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the complexes of the APP processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

### **2. BACKGROUND OF THE INVENTION**

Alzheimer's disease is a chronic condition that affects millions of individuals worldwide. After onset of the disease sufferers require a high degree of supervision and care. As the proportion of aged individuals in the population increases, the number of sufferers of Alzheimer's disease is expected to expand dramatically. Current top drugs (e.g. Aricept®/donepezil) attempt to achieve a temporary improvement of cognitive functions by inhibiting acetylcholinesterase, which results in increased levels of the neurotransmitter acetylcholine in the brain. These therapies are not suitable for later stages of the disease, they do not treat the underlying disease pathology, and they do not halt disease progression. The growing need for an effective therapy, coupled with the absence of effective treatments, presents a significant opportunity for drug target development and drug discovery.

The brains of sufferers of Alzheimer's disease show a characteristic pathology of prominent neuropathologic lesions, such as the initially intracellular neurofibrillary tangles (NFTs), and the extracellular amyloid-rich senile plaques. These lesions are associated with massive loss of populations of CNS neurons and their progression accompanies the clinical dementia associated with AD. The major component of amyloid plaques is the amyloid beta peptide. Amyloid beta is the proteolytic product of a precursor protein, beta amyloid precursor protein (beta-APP or APP). APP is a type-I trans-membrane protein which is cleaved by several different membrane-associated proteases. The first cleavage of APP occurs extracellularly by one of two proteases, alpha-secretase or beta-secretase. Beta-secretase or BACE1 (beta-site APP-cleaving enzyme) is a type-I transmembrane protein containing an aspartyl protease activity (described in detail below). Alpha secretase is a metalloprotease whose activity is most likely to be provided

by one or a combination of the proteins ADAM10 and ADAM17. Following either the beta or alpha cleavage of APP, the final cleavage event occurs within the membrane and is carried out by a protein complex called gamma secretase. It is the combination of the beta and gamma secretase activities that results in the liberation of the Abeta peptides of 40 and 42 residues (there are also lower levels of other forms) from the APP and ultimately the formation of the amyloid plaques responsible for the pathology of Alzheimer's disease. It is believed that the Abeta-42 peptide is the most critical Abeta species, because it shows the most pronounced neurotoxicity, and can aggregate easily, thus forming a nucleus for the aggregation of other Abeta peptides, such as the Abeta-40 which is typically produced at higher levels than the other species.

The applicant's proprietary proteomics technology (TAP/LC-MS/MS) is particularly successful in the elucidation of membrane protein complexes. These multiprotein complexes form the core of the APP processing pathway and are not amenable to other techniques. Known proteins with an important functional role in APP processing were analysed with The applicant's technology to comprehensively chart the dynamic protein interactions that contribute to Abeta production. Selected novel targets are subsequently validated using cellular or biochemical assays. Moreover, purified multi-protein complexes (e.g. beta- or gamma-secretase) do represent defined functional molecular machines, which are used to evaluate the mechanism of known compounds and for the optimisation of leads.

### **Presenilins**

Presenilins 1 and 2 (PS1 and PS2) are integral membrane proteins which are localised in the endoplasmic reticulum, the Golgi and also at the cell surface [1]. They are predominantly found as a heterodimers of the NTF and CTF endoproteolytic fragments. The protease that cleaves presenilins (the "presenilinase") is not known, it is likely that the process is autocatalytic, also the functional significance of PS (auto)proteolysis is unclear.

Presenilins are involved in the proteolytical processing of Amyloid precursor protein (APP) [2] and the Notch receptor [3, 4]. In addition, Presenilins are associated with the cell-adhesion proteins alpha and beta-catenin, N-cadherin, and E-cadherin [5] [6] and other members of the armadillo family [7] [8] [9] [10].

APP processing by Presenilins is through their effects on gamma-secretase which cleaves APP, generating the C-terminus of the A-beta peptide. PS1 associates with the C83 and C99 processed C-terminal fragments of APP [11], Nicastrin [12] and Pen-2 [13]. Aph-1 [14] [13] is required in Presenilin processing. It is not clear whether Presenilins regulate gamma-secretase activity directly or whether they are protease enzymes themselves [15]. The gamma secretase activity could comprise a multimeric complex of these proteins [12] [16] but it is not known how the relationship between these proteins affects secretase activity.

Familial Alzheimer's disease (FAD) patients carry mutations in the presenilin proteins (PS1; PS2) or in APP. These mutations result in increased production of A-beta42 [17] which is the main component of cerebral plaques in FAD [18].

Understanding the composition of the gamma-secretase complex, the relationship between its component parts and its regulation are important in the design of drugs for use in Alzheimer's disease patients.

### Nicastrin

Nicastrin is a type 1 trans-membrane glycoprotein with a conserved transmembrane domain and DYIGS motif [12] which is constitutively expressed in neural cell lines [19]. Biochemical studies have shown that Nicastrin binds to Presenilins 1 and 2, C-terminal derivatives of APP [12], membrane-tethered forms of Notch [20] and that it is a member of the gamma-secretase complex along with PS1 and PS2 [16]. Gamma secretase activity is involved in the cleavage of both Notch and APP. It has been shown that Nicastrin is required for the intra-membrane cleavage of Notch [21] and APP [22], it may also have a role in post-translational stabilisation of Presenilin [23].

Aph-1 [14] and Pen-2 [13] were cloned recently in a screen for presenilin enhancers ("pen") in *C. elegans* and shown to interact genetically with Aph-2 (Nicastrin). Defects in Aph-1 affect Notch signalling and Nicastrin localisation [14]. Aph-1 and Pen-2 are required for Notch cleavage, gamma-secretase activity and the accumulation of processed Presenilins. Francis et al. [13] cloned the putative human orthologues of these genes, Aph-1a, Aph-1b and Pen-2, and recently Lee et al. [24] also cloned the human Aph-1 cDNAs.

The exact components of the gamma-secretase complex are not known but these two novel proteins could be components of or accessory factors to the complex and may interact together directly with Presenilin or with a Presenilin/Nicastrin complex. Nicastrin

is therefore a member of the active gamma-secretase complex and there is recent evidence that it is the fully glycosylated form of the protein which is important in this complex. [25-29]

### **Aph-1**

Goutte et al. [14] cloned aph-1 from *C. elegans*. Aph-1 encodes a novel conserved membrane protein with seven hydrophobic regions which are predicted to be membrane spanning. It has a 40 amino acid hydrophilic tail. *C. elegans* aph1 mutants have a phenotype which is indicative of a defect in Notch signalling. In these mutants, Aph-2 (Nicastrin) localisation is altered from being at the cell surface to being in the cytoplasm, concentrated around the nucleus. In *C. elegans*, Aph-1 interacts genetically with Aph-2 (Nicastrin) and Sel-12 (one of the *C. elegans* Presenilin genes) [13].

There are Human, Mouse, *Drosophila* Aph-1 homologues which are potential orthologues. Recently, the human Aph-1 homologues, hAph-1a and hAph-1b have been cloned [13, 24]. Aph-1a, the hypothetical CGI-78 protein, and Sambiasin-1 isolated by the applicant are all products of the same gene. Francis et al [13] showed that Aph-1 and Pen-2 are required for Notch cleavage, gamma-secretase activity and the accumulation of processed Presenilins in cultured *Drosophila* cells.

Lee et al. [24] cloned two splice variants of Aph-1a called Aph-1aS and Aph-1aL and Aph-1b. They have shown that mammalian Aph-1aL associates with Nicastrin and PS1 NTF/CTF heterodimers and with PS2 and Nicastrin in cultured cells and that endogenous Aph1aL associates with Nicastrin and PS1 in rat brain. Inhibition of the expression of Aph1a reduces the expression of both PS1 and PS2 but not Nicastrin and results in the accumulation of gamma-secretase substrates and the reduction of Abeta. Aph1a was also shown to be required for Notch cleavage.

Aph-1 may have a role in the maturation and trafficking of Nicastrin but it is necessary for gamma-secretase function and may be a member of the gamma-secretase complex.

### **Pen-2**

Francis et al. [13] isolated pen-1 and pen-2 as two presenilin enhancer genes in a genetic screen in *C. elegans*. Pen-1 is identical to Aph-1 [14]. Pen-2 has two transmembrane domains and is thought to be a polytopic integral membrane protein. This group cloned the human homologues of Aph-1 and Pen-2. In *C. elegans*, Aph-1 and

Pen-2 interact genetically with Aph-2 (Nicastrin) but not with each other. Hop-1 and Sel-12 are the *C.elegans* presenilin genes. Aph-2 interacts with Hop-1 whereas Aph-1 and Pen-2 interact with Sel-12 [13].

Pen-2 associates with PS1, PS2 and Nicastrin in mammalian cells and Aph-1 and Pen-2 are required for Notch cleavage, gamma-secretase activity and the accumulation of processed Presenilins in cultured *Drosophila* cells [13].

Nicastrin maturation is affected by the levels of PS1 and Pen-2. Loss of PS1 or a reduction in expression of Nicastrin reduces Pen-2 protein levels and a reduction in expression of Pen-2 decreases levels of both PS1, PS2 proteins. In addition, reducing the expression of Pen-2 by RNAi reduces the level of the PS1 complex [30]. These data suggest that Pen-2 is either a component of or regulates the assembly of the PS1 complex and that the expression of these proteins is co-ordinately regulated.

#### **BACE1 (beta-secretase)**

Vassar et al. [31] cloned a transmembrane aspartic protease that had the characteristics of the postulated beta-secretase of APP. Three other groups also cloned BACE1 using different approaches. BACE1 knockout mice have a normal phenotype, suggesting that therapeutic inhibition of BACE1 for AD may be free of mechanism-based toxicity. BACE1 <sup>-/-</sup> mice who are also homozygous for an amyloid precursor protein transgene lack brain beta-amyloid and beta-secretase-cleaved APP C-terminal fragments. [32]. Brain and primary cortical cultures from BACE1 knockout mice showed no detectable beta-secretase activity, and primary cortical cultures from BACE knockout mice produced much less amyloid-beta from APP. This suggests that BACE1, rather than its paralogue BACE2, is the main beta-secretase for APP.

BACE1 is a protein of 501 amino acids containing a 21-aa signal peptide followed by a proprotein domain spanning aa 22 to 45. There are alternatively spliced forms, BACE-I-457 and BACE-I-476. The luminal domain of the mature protein is followed by one predicted transmembrane domain and a short cytosolic C-terminal tail of 24 aa. BACE1 is predicted to be a type 1 transmembrane protein with the active site on the luminal side of the membrane, where beta-secretase cleaves APP and possible other yet unidentified substrates. BACE1 mRNA in rat brain is present at higher levels in neurons than in glia, supporting that neurons are the primary source of the extracellular A-beta deposited in plaques. Sequence and mass spectrometry analyses showed that asn153, asn172, asn223, and asn354 of the BACE1 ectodomain are N-glycosylation

sites. In addition, the ectodomain contains 6 cys residues that form disulfide bridges between positions 216 and 420, 278 and 443, and 330 and 380. The C-terminal domain of BACE1 contains a dileucine motif (LL499/500) that can potentially regulate its trafficking and endocytosis, and an adjacent serine, which is a casein kinase 1 phosphorylation site (S498) [33]. The propeptide is predominantly cleaved from BACE1 by furin [34]. In cells expressing wt or Swedish mutant APP, transient overexpression of BACE1 decreased alpha-secretase cleavage and increased beta-secretase activity at the known beta-secretase positions, asp1 and glu11. Although BACE1 is clearly a key enzyme required for the processing of APP into Ab, other potential substrates and functions of BACE1 are unknown. Also, no BACE1 interacting proteins with regulatory or modulatory functions have been described. Proteins that activate BACE1 activity would form suitable intervention points for Alzheimer's disease therapy. In addition, proteins that inhibit BACE1, like substrates or pseudosubstrates, could also provide suitable means of intervention e.g. as proteins therapeutics.

### **APP**

APP is the precursor of Abeta, a peptide which forms the principal component of Alzheimer disease (AD) senile plaques [35] Masters et al. purified the cerebral amyloid protein that forms the plaque core in AD and Down syndrome. Van Nostrand et al. [36] presented evidence that nexin-II, a protease inhibitor that is synthesized and secreted by extravascular cells, is identical to APP. Multhaup et al. [37] demonstrated that APP is involved in copper reduction. They postulated that copper-mediated toxicity may contribute to neurodegeneration in AD, possibly by increased production of hydroxyl radicals. Yan et al. [38] reported that the receptor for advanced glycation end products RAGE is a receptor for the a-beta peptide and that expression of this receptor increases in AD. Expression of RAGE is particularly increased in neurons close to deposits of amyloid beta peptide and to neurofibrillary tangles. Kaneko et al. [39] demonstrated that nanomolar concentrations of various synthetic beta amyloids specifically impaired mitochondrial succinate dehydrogenase, and speculated that one of the primary targets of beta amyloids is the mitochondrial electron transport chain.

Several missense mutations in the APP gene have been identified that result in early-onset AD: the Swedish APP670/671 double mutation; 3 different mutations at codon 717: the London APP717 mutation, V717I, V717F, and V717G; and the Florida APP716 mutation (Reviewed by Bertram and Tanzi [40]). Most of these AD-related

mutations involve amino acid changes near the beta- and gamma-secretase cleavage sites. Two other missense mutations in the APP gene are located within A-beta near the alpha-secretase cleavage site: the Flemish APP692 mutation, which is associated with cerebral hemorrhage due to congophilic amyloid angiopathy or with early-onset AD with onset age in the mid-forties; and the Dutch APP693 mutation. Almost all AD-linked mutations do elevate secretion of A-beta-42, however, APP693 does not. [41]

Cao and Sudhof [42] demonstrated that the cytoplasmic tail of APP forms a complex with the nuclear adaptor protein Fe65 and the histone acetyltransferase TIP60. This complex stimulates transcription via heterologous Gal4 or LexA DNA binding domains, suggesting that release of the cytoplasmic tail of APP by gamma-cleavage may function in gene expression. The complex could modify expression of genes that function in inflammation [43] or apoptosis [44].

Weggen et al. [45] reported that the nonsteroidal antiinflammatory drugs ibuprofen, indomethacin, and sulindac can decrease the levels of high amyloidogenic amyloid-beta-42 peptide produced from a variety of cultured cells by as much as 80%. This effect was not seen in all NSAIDs and seemed not to be mediated by inhibition of cyclooxygenase (Cox) activity. Weggen et al. (2001) also demonstrated that short-term administration of ibuprofen to mice that produce APP lowered their brain levels of amyloid-beta-42. In cultured cells, the decrease in amyloid-beta-42 secretion was accompanied by an increase in the amyloid-beta(1-38) isoform, indicating that NSAIDs subtly alter gamma-secretase activity without significantly perturbing other APP processing pathways or Notch cleavage.

Proteins and other factors that regulate APP processing, and especially those that influence levels of Abeta-42 versus other Abeta species, form important potential targets in AD therapy.

### **Calsenilin**

In a yeast two-hybrid screen with the C-terminus of Presenilin 2, a neuronal EF-hand (calcium-binding) protein was identified and named "calsenilin" [46]. It interacted with both Presenilin 1 and Presenilin 2 in cells and regulated the levels of a proteolytic product of Presenilin 2. Calsenilin is identical to KChIP3, a protein which was found in a yeast two-hybrid screen for proteins interacting with A-type potassium channels (Kv4.3) [47]. KChIP3 i) increased the density of Kv4.2 currents indicating a stabilisation of the

channels at the plasma membrane; ii) shifted the current to hyperpolarized potentials; iii) slowed down the kinetics of inactivation and increased the kinetics of recovery. Calsenilin is also identical to the transcriptional repressor DREAM which acts constitutively to suppress prodynorphin expression in spinal cord neurons [48]. Knocking out DREAM results in sufficient dynorphin expression to produce a strong reduction in generalized pain behavior, highlighting the role that intracellular molecules play in modulating pain gating in the spinal cord. Hence proteins that modulate Calsenilin/DREAM activity are interesting targets in nociception.

### Tau

Neurofibrillary tangles (NFT), intraneuronal tau protein deposits, are hallmarks of several neurodegenerative disorders such as Alzheimer's and Pick's disease, frontotemporal dementia, cortico-basal degeneration and progressive supranuclear palsy.

The seven tau isoforms are all products of a single gene. Alternative splicing gives rise to six mRNA species differentially expressed in the CNS, depending on stage of neuronal maturation and neuron type. Tau is found mainly in the axon whereas a related protein, MAP2, is mainly found in dendrites.

Tau and MAP2 are microtubule-associated proteins (MAPs) which coassemble with microtubules and colocalise with microtubules in cells. Tau is a nonstructured molecule with a microtubule binding site containing 3 or 4 characteristic amino acid repeat in its carboxyl-terminal half. Alonso et al. [49] noted that in the brains of AD patients the neuronal cytoskeleton is progressively disrupted and replaced by tangles of paired helical filaments (PHFs), and that PHFs are composed mainly of hyperphosphorylated forms of tau. They demonstrated that in solution normal tau associated with the hyperphosphorylated AD P-tau to form large tangles of filaments. They also demonstrated that dephosphorylation with alkaline phosphatase abolished the ability of AD P-tau to aggregate in vitro. In a form of autosomal dominant inherited dementia known as FTDP17 or Pick disease, the tau gene carries missense mutations or mutations in the 5'- splice site of exon 10, which results in increased levels of tau isoforms with 4 microtubule-binding repeats. These mutations lead to tau molecules that show reduced affinity for microtubules or are more prone to self aggregation.

Proteins and other factors that influence the affinity of tau protein for microtubules, and moreover, influence the aggregation of tau, which is probably mediated by

phosphorylation and dephosphorylation events, are important potential targets in AD therapy.

### **Fe65**

Fe65 is a PTB domain- and WW domain-containing adaptor protein that is part of protein complexes at the plasma membrane as well as in the nucleus: It interacts with the Alzheimer's disease amyloid precursor protein (APP; [50]) and related proteins APLP1 and APLP2 [51]. Binding of Fe65 to the cytoplasmic tail of APP enhances production of amyloid-forming Abeta peptides [52], but the molecular mechanism of this amyloidogenic effect of Fe65 has not been elucidated. Furthermore, Fe65 stabilizes AICD (APP Intracellular Domain), the cytosolic product of APP cleavage by gamma-secretase, [53] and forms a nuclear protein complex with TIP60 [42]. Little is known about the functional consequences of Fe65-dependent transactivation. The important role of TIP60 in interleukin-1beta- and NF-KappaB-dependent transactivation [43] suggests, however, that the Fe65 complex might function in inflammation.

Fe65 has been shown to bind to the transcription factor CP2/LSF/LBP1 [54] and the low-density lipoprotein receptor-related protein [55], but the significance of these interactions is unknown. Finally, Fe65 has been observed to block cell cycle progression by downregulating thymidylate synthase expression via an unknown mechanism [56].

Understanding the composition of the Fe65 complex, the relationship between its component parts and its regulation might therefore be important in the design of drugs for use in Alzheimer's disease patients as well as for the treatment of various inflammatory conditions and cancer.

### **X11beta**

X11beta/Mint-2 is a neuronal adaptor protein that is believed to be involved in signal transduction processes. It is also regarded as a putative vesicular trafficking protein in the brain that can form a complex with the potential to couple synaptic vesicle exocytosis to neuronal cell adhesion [57].

X11beta interacts with the Alzheimer's disease amyloid precursor protein (APP) [50]. Acting synergistically with Munc18a [58], X11beta stabilises APP and inhibits production of proteolytic APP fragments including the A beta peptide that is deposited in the brains of Alzheimer's disease patients [59].

Via a mechanism that depends on its PDZ domain (yet has otherwise not been characterized), X11beta potently inhibits transactivation by an APP-Gal4/VP16 fusion protein [58]. Besides interacting with APP, X11beta binds to the C-terminus of presenilin1, although not as strongly as does X11alpha [58]. In addition, X11beta has been reported to interact with XB51 [60], but the functional significance of this interaction is unknown.

In *Drosophila*, dX11beta overexpression in eye imaginal disks causes disruption of compound eye morphology due to enhanced apoptosis of neuronal cells [61]. X11beta has been shown to bind to NF-KappaB-p65 through its PDZ domain. This interaction has been implicated in NF-KappaB-dependent Abeta42 production [62].

Elucidation of X11beta complex composition and regulation might therefore help develop novel ways of therapeutic intervention in Alzheimer's disease and inflammation.

### **3. SUMMARY OF THE INVENTION**

An object of the present invention was to identify protein complexes of the beta-amyloid precursor protein (APP) processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the protein complexes of the APP processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

By applying the process according to the invention said complexes were identified. The components are listed in table 1.

Said object is further achieved by the characterization of component proteins. These proteins are listed in table 2.

Thus, the invention relates to the following embodiments:

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein, which first protein is selected from the group of proteins in table 1, fourth column of a given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant

of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and

(b) at least one second protein, which second protein is selected from the group of proteins in table 1, fifth column of said given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said second protein, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and a complex (II) comprising at least two of said second proteins,

wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. A protein complex comprising a first protein selected from the proteins listed in table 1, second column of a given complex or a homologue or variant thereof, or a functionally active fragment or functionally active derivative of said first protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said first protein under low stringency conditions, and at least one second protein selected from the group of proteins in table 1, fifth column of a given complex, or a variant or homologue thereof, or a functionally active fragment or a functionally active derivative of said second protein, the variant of said second protein being encoded by a nucleic acid that hybridizes to the nucleic acid of said second protein under low-stringency conditions, and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

3. A protein complex comprising all proteins selected from the proteins in table 1, third column of a given complex or at least one protein being a homologue thereof, or a variant thereof or functionally active fragment or functionally active derivative of said protein, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low stringency conditions;  
wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
4. A protein complex that comprises all proteins as listed in table 1, third column for a given complex or at least one protein being a homologue or a variant thereof, or a functionally active fragment or a functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins under low stringency conditions, except at least one protein of the proteins listed in table 5, third column, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C, with the proviso that the complex comprises at least one protein selected from table 1, fifth column of a given complex.
5. The complex of any of No. 1 - 4 comprising at least one functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in at least one biochemical activity as stated in table 3.
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:  
expressing a protein of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the protein, preferably the tagged protein, and optionally disassociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of a protein complex obtainable by a process according to any of No. 9 - 11.
13. Protein selected from the group of proteins in table 1, sixth column of a given complex or a homologue or a variant of thereof, or a functionally active fragment or a functionally active derivative of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X

SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to No. 13.
15. Construct, preferably a vector construct, comprising
  - (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
  - (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, at least one of said proteins being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, being selected from the second group of proteins according to No. 1 (b) or
  - (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.
16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and /or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid encoding at least one protein selected from the first group of proteins according to No. 1 (a) and at least one nucleic acid encoding at least one protein selected from the second group of proteins according to No. 1 (b).
17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody containing the binding domain thereof which binds to any of the proteins of the group of proteins according to No. 13.
18. A kit comprising in one or more containers:
  - (a) the complex of any of No. 1 - 8 and/or the proteins of No. 13 and/or
  - (b) an antibody according to No. 17 and/or

- (c) a nucleic acid encoding a protein of the complex of any of No. 1 – 8 and/or a protein of No. 13 and/or
- (d) cells expressing the complex of any of No. 1 – 8 and/or a protein of No. 13 and, optionally,
- (e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of a complex of any one of No. 1 - 8.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 13 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for modifying a substrate of a complex of any one of No. 1 - 8 comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or a protein according to No. 13.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders, preferentially for diseases or disorders such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to a complex of any one of No. 1 - 8 and/or a protein of No. 13, comprising the following steps:

- (a) exposing said complex or protein, or a cell or organism containing said complex or said protein, to one or more candidate molecules; and
- (b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:

- (a) exposing said complex, or a cell or organism containing said complex to one or more candidate molecules; and
- (b) determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent upon the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity, or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether any of the proteins listed in table 1, third column of said complex, or a functionally active fragment or a functionally active derivative thereof, or a variant or a homologue thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low-stringency conditions, is present in the complex.
32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder, preferentially of a disease or disorder selected from the diseases or disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
34. A method for the production of a pharmaceutical composition comprising carrying out the method of No. 26 - 31 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, component disposition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicated the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.
37. The method of No. 35, wherein the activity of said complex is determined.
38. The method of No. 37, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.
40. The method of No. 39, wherein said determining step comprises determining whether any of the proteins according to No. 13 is present in the complex.
41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment thereof of No. 17, for use in a method of diagnosing a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity of, component composition of or intracellular localization of, the complex of any one of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, activity of, or protein composition of, said complex.
43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.
45. Complex of No. 1 - 8 and/or a protein as listed in table 1, fifth column of said complex as a target for an active agent of a pharmaceutical, preferably a drug target, in the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

### 3.1 DEFINITIONS

The term "activity" as used herein, refers to the function of a molecule in its broadest sense. It generally includes, but is not limited to, biological, biochemical, physical or chemical functions of the molecule. It includes for example the enzymatic activity, the ability to interact with other molecules and ability to activate, facilitate, stabilize, inhibit, suppress or destabilize the function of other molecules, stability, ability to localize to certain subcellular locations. Where applicable, said term also relates to the function of a protein complex in its broadest sense.

The term "agonist" as used herein, means a molecule which modulates the formation of a protein complex or which, when bound to a complex or protein of the invention or a molecule in the protein complex, increases the amount of, or prolongs the duration of, the activity of the complex. The stimulation may be direct or indirect, including effects on the expression of a gene encoding a member of the protein complex, or by a competitive or non-competitive mechanism. Agonists may include proteins, nucleic acids, carbohydrates or any other organic or inorganic molecule or

above mentioned degrees of percentages and concentration may be used to define an agonist of the invention, with greater effect at lower concentrations being preferred.

The term "amount" as used herein and as applicable to the embodiment described relates to the amount of the particular protein or protein complex described, including the value of null, i.e. where no protein or protein complex described in that particular embodiment is present under the or any of the conditions which might be specified in that particular embodiment.

The term "animal" as used herein includes, but is not limited to mammals, preferably mammals such as cows, pigs, horses, mice, rats, cats, dogs, sheep, goats and most preferably humans. Other animals used in agriculture, such as chickens, ducks etc. are also included in the definition as used herein.

The term "animal" as used herein does not include humans if being used in the context of genetic alterations to the germline.

The term "antagonist" as used herein, means a molecule which modulates the formation of a protein complex or which, when bound to a complex or protein of the invention or a molecule in the protein complex, decreases the amount of, or the duration or level of activity of the complex. The effect may be direct or indirect, including effects on the expression of a gene encoding a member of the protein complex, or by a competitive or non-competitive mechanism. Antagonists may include proteins, including antibodies, nucleic acids, carbohydrates or any other organic or inorganic molecule or metals. Antagonists also include a functional peptide or peptide fragment derived from a protein member of the complexes of the invention or a protein member itself of the complexes of the invention. Preferred antagonists are those which, when added to the complex and/or the protein of the invention under physiological conditions and/or in vitro assays, including diagnostic or prognostic assays, result in a change of the level of any of the activities of the protein complex and/or the proteins of the invention as exemplary illustrated above by at least 10%, at least 20%, at least 30%, at least 40% at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% or at least 99% at a concentration of the inhibitor of  $1\mu\text{g ml}^{-1}$ ,  $10\mu\text{g ml}^{-1}$ ,  $100\mu\text{g ml}^{-1}$ ,  $500\mu\text{g ml}^{-1}$ ,  $1\text{mg ml}^{-1}$ ,  $10\text{mg ml}^{-1}$  or  $100\text{mg ml}^{-1}$ .

Any combination of the above mentioned degrees of percentages and concentration may be used to define antagonist of the invention, with greater effect at lower concentrations being preferred.

The term "antibodies" as used herein, include include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, Fab fragments, and an Fab expression library.

The term "binding" as used herein means a stable or transient association between two molecules, including electrostatic, hydrophobic, ionic and/or hydrogen-bond interaction under physiological conditions and/or conditions being used in diagnostic or prognostic method or process or procedure.

The term "carrier" as used herein refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are preferred carriers when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are preferably employed as liquid carriers for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the therapeutic, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

If not stated otherwise, the terms "complex" and "protein complex" are used interchangeably herein and refer to a complex of proteins that is able to perform one or more functions of the wild type protein complex. The protein complex may or may not include and/or be associated with other molecules such as nucleic acid, such as RNA or

DNA, or lipids or further cofactors or moieties selected from a metal ions, hormones, second messengers, phosphate, sugars.

A "complex" of the invention may also be part of or a unit of a larger physiological protein assembly.

The term "component of the APP processing pathway" as used herein refers to a protein and/or protein complex which is involved in mediating APP processing in a cell. Components of the APP processing pathway include the following protein complexes as provided herein and components thereof:

Presenilin 1 complex, Sambiasin complex, Presenilin 2 complex, Nicastrin complex, Aph-1a complex, Aph-1b complex, Pen-2 complex, BACE1 D215N complex, APP complex, APP695SW complex, APP-C99 complex, Tau complex, X11beta complex, Fe65 complex and Calsenilin complex.

If not stated otherwise, the term "compound" as used herein are include but are not limited to peptides, nucleic acids, carbohydrates, natural product extract librariesorganic molecules, preferentially small organic molecules, anorganic molecules, including but not limited to chemicals, metals and organometallic molecules.

The terms "derivatives" or "analogs of component proteins" or "variants" as used herein include, but are not limited, to molecules comprising regions that are substantially homologous to the component proteins, in various embodiments, by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99% identity over an amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art, or whose encoding nucleic acid is capable of hybridizing to a sequence encoding the component protein under stringent, moderately stringent, or nonstringent conditions. It means a protein which is the outcome of a modification of the naturally occurring protein, by amino acid substitutions, deletions and additions, respectively, which derivatives still exhibit the biological function of the naturally occurring protein although not necessarily to the same degree. The biological function of such proteins can e.g. be examined by suitable available in vitro assays as provided in the invention.

The term "functionally active" as used herein refers to a polypeptide, namely a fragment or derivative, having structural, regulatory, or biochemical functions of the protein according to the embodiment of which this polypeptide, namely fragment or derivative is related to.

The term "fragment" as used herein refers to a polypeptide of at least 10, 20, 30, 40 or 50 amino acids of the component protein according to the embodiment. In specific embodiments, such fragments are not larger than 35, 100 or 200 amino acids.

The term "gene" as used herein refers to a nucleic acid comprising an open reading frame encoding a polypeptide of, if not stated otherwise, the present invention, including both exon and optionally intron sequences.

The terms "homologue" or "homologous gene products" as used herein mean a protein in another species, preferably mammals, which performs the same biological function as the a protein component of the complex further described herein. Such homologues are also termed "orthologous gene products". The algorithm for the detection of orthologue gene pairs from humans and mammalians or other species uses the whole genome of these organisms. First, pairwise best hits are retrieved, using a full Smith-Waterman alignment of predicted proteins. To further improve reliability, these pairs are clustered with pairwise best hits involving *Drosophila melanogaster* and *C. elegans* proteins. Such analysis is given, e.g., in Nature, 2001, 409:860-921. The homologues of the proteins according to the invention can either be isolated based on the sequence homology of the genes encoding the proteins provided herein to the genes of other species by cloning the respective gene applying conventional technology and expressing the protein from such gene, or by isolating proteins of the other species by isolating the analogous complex according to the methods provided herein or to other suitable methods commonly known in the art.

The term "host cells" or, where applicable, "cells" or "hosts" as used herein is intended to be understood in a broadest sense and include, but are not limited to mammalian cell systems infected with virus (e.g., vaccinia virus, adenovirus, etc.); insect cell systems infected with virus (e.g., baculovirus); microorganisms such as yeast containing yeast vectors; or bacteria transformed with bacteriophage, DNA, plasmid DNA, or cosmid DNA. The expression elements of vectors vary in their strengths and specificities. Depending on the host-vector system utilized, any one of a number of suitable transcription and translation elements may be used. It is understood that this term not only refers to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation of environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

The term "modification" as used herein refers to all modifications of a protein or protein complex of the invention including cleavage and addition or removal of a group.

The term "nucleic acid" as used herein refers to polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). They may also be polynucleotides which include within them synthetic or modified nucleotides. A number of different types of modification to polynucleotides are known in the art. These include methylphosphonate and phosphorothioate backbones, addition of acridine or polylysine chains at the 3' and/or 5' ends of the molecule. For the purposes of the present invention, it is to be understood that the polynucleotides described herein may be modified by any method available in the art. Such modifications may be carried out in order to enhance the *in vivo* activity or lifespan of polynucleotides of the invention. Polynucleotides according to the invention may be produced recombinantly, synthetically, or by any means available to those of skill in the art. They may also be cloned by standard techniques. The polynucleotides are typically provided in isolated and/or purified form. As applicable to the embodiment being described, they include both single stranded and double-stranded polynucleotides.

The term "percent identity", as used herein, means the number of identical residues as defined by an optimal alignment using the Smith-Waterman algorithm divided by the length of the overlap multiplied by 100. The alignment is performed by the search program (Pearson, 1991, *Genomics* 11:635-650) with the constraint to align the maximum of both sequences.

The terms "polypeptides" and "proteins" are, where applicable, used interchangeably herein. They may be chemically modified, e.g. post-translationally modified. For example, they may be glycosylated or comprise modified amino acid residues. They may also be modified by the addition of a signal sequence to promote their secretion from a cell where the polypeptide does not naturally contain such a sequence. They may be tagged with a tag. They may be tagged with different labels which may assist in identification of the proteins in a protein complex. Polypeptides/proteins for use in the invention may be in a substantially isolated form. It will be understood that the polypeptide/protein may be mixed with carriers or diluents which will not interfere with the intended purpose of the polypeptide and still be regarded as substantially isolated. A polypeptide/protein for use in the invention may also be in a substantially purified form, in which case it will generally comprise the polypeptide in a

preparation in which more than 50%, e.g. more than 80%, 90%, 95% or 99%, by weight of the polypeptide in the preparation is a polypeptide of the invention.

"Target for therapeutic drug" means that the respective protein (target) can bind the active ingredient of a pharmaceutical composition and thereby changes its biological activity in response to the drug binding.

The term "tag" as used herein is meant to be understood in its broadest sense and to include, but is not limited to any suitable enzymatic, fluorescent, or radioactive labels and suitable epitopes, including but not limited to HA-tag, Myc-tag, T7, His-tag, FLAG-tag, Calmodulin binding proteins, glutathione-S-transferase, strep-tag, KT3-epitope, EEF-epitopes, green-fluorescent protein and variants thereof.

The term "therapeutics" as used herein, includes, but is not limited to, a protein complex of the present invention, the individual component proteins, and analogs and derivatives (including fragments); antibodies thereto; nucleic acids encoding the component protein, and analogs or derivatives thereof; component protein antisense nucleic acids, and agents that modulate complex formation and/or activity (i.e., agonists and antagonists).

The term "vector" as used herein means a nucleic acid molecule capable of transporting another nucleic acid sequence to which it has been linked. Preferred vectors are those capable of autonomous replication and/or expression of nucleic acids to which they linked. The terms "plasmid" and "vector" are used interchangeably herein when applicable to the embodiment. However, vectors other than plasmids are also included herein. The expression elements of vectors vary in their strengths and specificities. Depending on the host-vector system utilized, any one of a number of suitable transcription and translation elements may be used.

#### **4. DETAILED DESCRIPTION OF THE INVENTION**

##### **Overview:**

An object of the present invention was to identify protein complexes of the beta-amyloid precursor protein (APP) processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the protein

complexes of the APP processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

By applying the process according to the invention said protein complex were identified. The components are listed in table 1.

Said object is further achieved by the characterisation of component proteins. These proteins are listed in table 2.

The invention thus relates to the following embodiments:

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein, which first protein is selected from the group of proteins in table 1, fourth column of a given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and
  - (b) at least one second protein, which second protein is selected from the group of proteins in table 1, fifth column of said given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said second protein, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
2. A protein complex comprising a first protein selected from the proteins listed in table 1, second column of a given complex or a homologue or variant thereof, or a functionally active fragment or functionally active derivative of said first protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said first

protein under low stringency conditions, and at least one second protein selected from the group of proteins in table 1, fifth column of a given complex, or a variant or homologue thereof, or a functionally active fragment or a functionally active derivative of said second protein, the variant of said second protein being encoded by a nucleic acid that hybridizes to the nucleic acid of said second protein under low-stringency conditions, and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

3. A protein complex comprising all proteins selected from the proteins in table 1, third column of a given complex or at least one protein being a homologue thereof, or a variant thereof or functionally active fragment or functionally active derivative of said protein, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low stringency conditions; wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
4. A protein complex that comprises all proteins as listed in table 1, third column for a given complex or at least one protein being a homologue or a variant thereof, or a functionally active fragment or a functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins under low stringency conditions, except at least one protein of the proteins listed in table 5, third column, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon

sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C, with the proviso that the complex comprises at least one protein selected from table 1, fifth column of a given complex.

5. The complex of any of No. 1 - 4 comprising at least one functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in at least one biochemical activity as stated in table 3.
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:  
expressing a protein of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the protein, preferably the tagged protein, and optionally disassociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of a protein complex obtainable by a process according to any of No. 9 - 11.
13. Protein selected from the group of proteins in table 1, sixth column of a given complex or a homologue or a variant of thereof, or a functionally active fragment or a functionally active derivative of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
14. Nucleic acid encoding a protein according to No. 13.
15. Construct, preferably a vector construct, comprising
  - (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
  - (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, at least one of said proteins being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, being selected from the second group of proteins according to No. 1 (b) or
  - (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and /or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid encoding at least one protein selected from the first group of proteins according to No. 1 (a) and at least one nucleic acid encoding at least one protein selected from the second group of proteins according to No. 1 (b).
17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody containing the binding domain thereof which binds to any of the proteins of the group of proteins according to No. 13.
18. A kit comprising in one or more containers:
- (a) the complex of any of No. 1 – 8 and/or the proteins of No. 13 and/or
  - (b) an antibody according to No. 17 and/or
  - (c) a nucleic acid encoding a protein of the complex of any of No. 1 – 8 and/or a protein of No. 13 and/or
  - (d) cells expressing the complex of any of No. 1 – 8 and/or a protein of No. 13 and, optionally,
  - (e) further components such as reagents, buffers and working instructions.
19. The kit according to No. 18 for processing a substrate of a complex of any one of No. 1 - 8.
20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 13 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for modifying a substrate of a complex of any one of No. 1 - 8 comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.
23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or a protein according to No. 13.
24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders, preferentially for diseases or disorders such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
25. A method for screening for a molecule that binds to a complex of any one of No. 1 - 8 and/or a protein of No. 13, comprising the following steps:
- (a) exposing said complex or protein, or a cell or organism containing said complex or said protein, to one or more candidate molecules; and
  - (b) determining whether said candidate molecule is bound to the complex or protein.
26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:
- (a) exposing said complex, or a cell or organism containing said complex to one or more candidate molecules; and
  - (b) determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent upon the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules

indicates that the molecule modulates function, activity, or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.
28. The method of No. 26, wherein the activity of said complex is determined.
29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.
31. The method of No. 30, wherein said determining step comprises determining whether any of the proteins listed in table 1, third column of said complex, or a functionally active fragment or a functionally active derivative thereof, or a variant or a homologue thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low-stringency conditions, is present in the complex.
32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder, preferentially of a disease or disorder selected from the diseases or disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of No. 26 - 31 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, component disposition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicated the presence in the subject of the disease or disorder or predisposition in the subject.
36. The method of No. 35, wherein the amount of said complex is determined.
37. The method of No. 35, wherein the activity of said complex is determined.
38. The method of No. 37, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.
40. The method of No. 39, wherein said determining step comprises determining whether any of the proteins according to No. 13 is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment thereof of No. 17, for use in a method of diagnosing a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity of, component composition of or intracellular localization of, the complex of any one of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, activity of, or protein composition of, said complex.
43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.
44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.
45. Complex of No. 1 - 8 and/or a protein as listed in table 1, fifth column of said complex as a target for an active agent of a pharmaceutical, preferably a drug target, in the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

Animal models are also provided herein.

Preferably, the protein components of the complexes described herein are all mammalian proteins. The complexes can also consist only of the respective homologues from other mammals such as mouse, rat, pig, cow, dog, monkey, sheep or horse or other species such as *D. melanogaster*, *C. elegans* or chicken. In another preferred embodiment, the complexes are a mixture of proteins from two or more species.

**TABLES:**

**Table 1: Composition of Complexes**

First column ('Name of complex'): Lists the name of the protein complexes as used herein.

Second column ('Entry point'): Lists the bait proteins that have been chosen for the purification of the given complex.

Third column ('All interactors'): Lists all novel interactors which have been identified as members of the complex and all interactors which have been known to be associated with the bait so far.

Fourth column ('Known interactors'): Lists all interactors which have been known to be associated with the bait so far.

Fifth column ('Novel interactors of the complex'): Lists all novel interactors of the complex which have been identified in the experiments provided herein.

Sixth column: Separately lists the members of the newly identified complex which have not been annotated previously.

**Table 2: Individual Proteins of the Complexes**

First column ('Protein'): Lists in alphabetical order all proteins which have been identified as interactors of the complexes presented herein.

Second column ('SEQ ID'): Lists the SEQ ID (Sequence Identifications) of the proteins herein as used herein.

Third column ('IPI-Numbers'): Lists the IPI-Numbers of the proteins herein. The IPI-Numbers refer to the International Protein Index created by the European Bioinformatics Institute (EMBL-EBI), Hinxton, UK.

Fourth column ('Molecular Weight'): Lists the Molecular Weight of the proteins in Dalton.

**Table 3: Biochemical Activities of the Complexes of the invention.**

First column ('Name of complex'): Lists the name of the protein complexes as used herein.

Second column ('Biochemical Activity'): Lists biochemical activities of the complexes. Assays in order to test these activities are also provided herein (infra).

**4.1 PROTEIN COMPLEXES/PROTEINS OF THE INVENTION**

The protein complexes of the present invention and their component proteins are described in the Tables 1 - 3. The protein complexes and component proteins can be obtained by methods well known in the art for protein purification and recombinant protein expression. For example, the protein complexes of the present invention can be isolated using the TAP method described in Section 5, *infra*, and in WO 00/09716 and Rigaut et al., 1999, *Nature Biotechnol.* 17:1030-1032, which are each incorporated by reference in their entirety. Additionally, the protein complexes can be isolated by immunoprecipitation of the component proteins and combining the immunoprecipitated proteins. The protein complexes can also be produced by recombinantly expressing the component proteins and combining the expressed proteins.

The nucleic and amino acid sequences of the component proteins of the protein complexes of the present invention are provided herein (SEQ ID NO 1 - 268), and can be obtained by any method known in the art, e.g., by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of each sequence, and/or by cloning from a cDNA or genomic library using an oligonucleotide specific for each nucleotide sequence.

Homologues (e.g., nucleic acids encoding component proteins from other species) or other related sequences (e.g., variants, paralogs) which are members of a native cellular protein complex can be obtained by low, moderate or high stringency hybridization with all or a portion of the particular nucleic acid sequence as a probe, using methods well known in the art for nucleic acid hybridization and cloning.

Exemplary moderately stringent hybridization conditions are as follows: prehybridization of filters containing DNA is carried out for 8 hours to overnight at 65°C in buffer composed of 6X SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 µg/ml denatured salmon sperm DNA. Filters are hybridized for 48 hours at 65°C in prehybridization mixture containing 100 µg/ml denatured salmon sperm DNA and 5-20 X 10<sup>6</sup> cpm of <sup>32</sup>P-labeled probe. Washing of filters is done at 37°C for 1 hour in a solution containing 2X SSC, 0.01% PVP, 0.01% Ficoll, and 0.01% BSA. This is followed by a wash in 0.1X SSC at 50°C for 45 min before autoradiography. Alternatively, exemplary conditions of high stringency are as follows: e.g., hybridization to filter-bound DNA in 0.5 M NaHPO<sub>4</sub>, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1xSSC/0.1% SDS at 68°C (Ausubel et al., eds., 1989, *Current Protocols in Molecular Biology*, Vol. I, Green Publishing Associates, Inc., and John Wiley & sons, Inc., New York, at p. 2.10.3). Other conditions of high stringency which may be

used are well known in the art. Exemplary low stringency hybridization conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 µg/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

For recombinant expression of one or more of the proteins, the nucleic acid containing all or a portion of the nucleotide sequence encoding the protein can be inserted into an appropriate expression vector, i.e., a vector that contains the necessary elements for the transcription and translation of the inserted protein coding sequence. The necessary transcriptional and translational signals can also be supplied by the native promoter of the component protein gene, and/or flanking regions.

A variety of host-vector systems may be utilized to express the protein coding sequence. These include but are not limited to mammalian cell systems infected with virus (e.g., vaccinia virus, adenovirus, etc.); insect cell systems infected with virus (e.g., baculovirus); microorganisms such as yeast containing yeast vectors; or bacteria transformed with bacteriophage DNA, plasmid DNA, or cosmid DNA. The expression elements of vectors vary in their strengths and specificities. Depending on the host-vector system utilized, any one of a number of suitable transcription and translation elements may be used.

In a preferred embodiment, a complex of the present invention is obtained by expressing the entire coding sequences of the component proteins in the same cell, either under the control of the same promoter or separate promoters. In yet another embodiment, a derivative, fragment or homologue of a component protein is recombinantly expressed. Preferably the derivative, fragment or homologue of the protein forms a complex with the other components of the complex, and more preferably forms a complex that binds to an anti-complex antibody. Such an antibody is further described infra.

Any method available in the art can be used for the insertion of DNA fragments into a vector to construct expression vectors containing a chimeric gene consisting of appropriate transcriptional/translational control signals and protein coding sequences. These methods may include in vitro recombinant DNA and synthetic techniques and in vivo recombinant techniques (genetic recombination). Expression of nucleic acid

sequences encoding a component protein, or a derivative, fragment or homologue thereof, may be regulated by a second nucleic acid sequence so that the gene or fragment thereof is expressed in a host transformed with the recombinant DNA molecule(s). For example, expression of the proteins may be controlled by any promoter/enhancer known in the art. In a specific embodiment, the promoter is not native to the gene for the component protein. Promoters that may be used can be selected from among the many known in the art, and are chosen so as to be operative in the selected host cell.

In a specific embodiment, a vector is used that comprises a promoter operably linked to nucleic acid sequences encoding a component protein, or a fragment, derivative or homologue thereof, one or more origins of replication, and optionally, one or more selectable markers (e.g., an antibiotic resistance gene).

In another specific embodiment, an expression vector containing the coding sequence, or a portion thereof, of a component protein, either together or separately, is made by subcloning the gene sequences into the EcoRI restriction site of each of the three pGEX vectors (glutathione S-transferase expression vectors; Smith and Johnson, 1988, Gene 7:31-40). This allows for the expression of products in the correct reading frame.

Expression vectors containing the sequences of interest can be identified by three general approaches: (a) nucleic acid hybridization, (b) presence or absence of "marker" gene function, and (c) expression of the inserted sequences. In the first approach, coding sequences can be detected by nucleic acid hybridization to probes comprising sequences homologous and complementary to the inserted sequences. In the second approach, the recombinant vector/host system can be identified and selected based upon the presence or absence of certain "marker" functions (e.g., resistance to antibiotics, occlusion body formation in baculovirus, etc.) caused by insertion of the sequences of interest in the vector. For example, if a component protein gene, or portion thereof, is inserted within the marker gene sequence of the vector, recombinants containing the encoded protein or portion will be identified by the absence of the marker gene function (e.g., loss of  $\beta$ -galactosidase activity). In the third approach, recombinant expression vectors can be identified by assaying for the component protein expressed by the recombinant vector. Such assays can be based, for example, on the physical or functional properties of the interacting species in in vitro assay systems, e.g., formation of a complex comprising the protein or binding to an anti-complex antibody.

Once recombinant component protein molecules are identified and the complexes or individual proteins isolated, several methods known in the art can be used to propagate them. Using a suitable host system and growth conditions, recombinant expression vectors can be propagated and amplified in quantity. As previously described, the expression vectors or derivatives which can be used include, but are not limited to, human or animal viruses such as vaccinia virus or adenovirus; insect viruses such as baculovirus, yeast vectors; bacteriophage vectors such as lambda phage; and plasmid and cosmid vectors.

In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, or modifies or processes the expressed proteins in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically-engineered component proteins may be controlled. Furthermore, different host cells have characteristic and specific mechanisms for the translational and post-translational processing and modification (e.g., glycosylation, phosphorylation, etc.) of proteins. Appropriate cell lines or host systems can be chosen to ensure that the desired modification and processing of the foreign protein is achieved. For example, expression in a bacterial system can be used to produce an unglycosylated core protein, while expression in mammalian cells ensures "native" glycosylation of a heterologous protein. Furthermore, different vector/host expression systems may effect processing reactions to different extents.

In other specific embodiments, a component protein or a fragment, homologue or derivative thereof, may be expressed as fusion or chimeric protein product comprising the protein, fragment, homologue, or derivative joined via a peptide bond to a heterologous protein sequence of a different protein. Such chimeric products can be made by ligating the appropriate nucleic acid sequences encoding the desired amino acids to each other by methods known in the art, in the proper coding frame, and expressing the chimeric products in a suitable host by methods commonly known in the art. Alternatively, such a chimeric product can be made by protein synthetic techniques, e.g., by use of a peptide synthesizer. Chimeric genes comprising a portion of a component protein fused to any heterologous protein-encoding sequences may be constructed.

In particular, protein component derivatives can be made by altering their sequences by substitutions, additions or deletions that provide for functionally equivalent molecules. Due to the degeneracy of nucleotide coding sequences, other DNA

sequences that encode substantially the same amino acid sequence as a component gene or cDNA can be used in the practice of the present invention. These include but are not limited to nucleotide sequences comprising all or portions of the component protein gene that are altered by the substitution of different codons that encode a functionally equivalent amino acid residue within the sequence, thus producing a silent change. Likewise, the derivatives of the invention include, but are not limited to, those containing, as a primary amino acid sequence, all or part of the amino acid sequence of a component protein, including altered sequences in which functionally equivalent amino acid residues are substituted for residues within the sequence resulting in a silent change. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity that acts as a functional equivalent, resulting in a silent alteration. Substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic) amino acids include arginine, lysine and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

In a specific embodiment, up to 1%, 2%, 5%, 10%, 15% or 20% of the total number of amino acids in the wild type protein are substituted or deleted; or 1, 2, 3, 4, 5, or 6 or up to 10 or up to 20 amino acids are inserted, substituted or deleted relative to the wild type protein.

In a specific embodiment of the invention, the nucleic acids encoding a protein component and protein components consisting of or comprising a fragment of or consisting of at least 6 (continuous) amino acids of the protein are provided. In other embodiments, the fragment consists of at least 10, 20, 30, 40, or 50 amino acids of the component protein. In specific embodiments, such fragments are not larger than 35, 100 or 200 amino acids. Derivatives or analogs of component proteins include, but are not limited, to molecules comprising regions that are substantially homologous to the component proteins, in various embodiments, by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99% identity over an amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art, or whose encoding nucleic acid is capable of

hybridizing to a sequence encoding the component protein under stringent, moderately stringent, or nonstringent conditions.

In a specific embodiment, proteins are provided herein, which share an identical region of 20, 30, 40, 50 or 60 contiguous amino acids of the proteins listed in table 2.

The protein component derivatives and analogs of the invention can be produced by various methods known in the art. The manipulations which result in their production can occur at the gene or protein level. For example, the cloned gene sequences can be modified by any of numerous strategies known in the art (Sambrook et al., 1989, *Molecular Cloning, A Laboratory Manual*, 2d Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York). The sequences can be cleaved at appropriate sites with restriction endonuclease(s), followed by further enzymatic modification if desired, isolated, and ligated in vitro. In the production of the gene encoding a derivative, homologue or analog of a component protein, care should be taken to ensure that the modified gene retains the original translational reading frame, uninterrupted by translational stop signals, in the gene region where the desired activity is encoded.

Additionally, the encoding nucleic acid sequence can be mutated in vitro or in vivo, to create and/or destroy translation, initiation, and/or termination sequences, or to create variations in coding regions and/or form new restriction endonuclease sites or destroy pre-existing ones, to facilitate further in vitro modification. Any technique for mutagenesis known in the art can be used, including but not limited to, chemical mutagenesis and in vitro site-directed mutagenesis (Hutchinson et al., 1978, *J. Biol. Chem.* 253:6551-6558), amplification with PCR primers containing a mutation, etc.

Once a recombinant cell expressing a component protein, or fragment or derivative thereof, is identified, the individual gene product or complex can be isolated and analyzed. This is achieved by assays based on the physical and/or functional properties of the protein or complex, including, but not limited to, radioactive labeling of the product followed by analysis by gel electrophoresis, immunoassay, cross-linking to marker-labeled product, etc.

The component proteins and complexes may be isolated and purified by standard methods known in the art (either from natural sources or recombinant host cells expressing the complexes or proteins), including but not restricted to column chromatography (e.g., ion exchange, affinity, gel exclusion, reversed-phase high pressure, fast protein liquid, etc.), differential centrifugation, differential solubility, or by

any other standard technique used for the purification of proteins. Functional properties may be evaluated using any suitable assay known in the art.

Alternatively, once a component protein or its derivative, is identified, the amino acid sequence of the protein can be deduced from the nucleic acid sequence of the chimeric gene from which it was encoded. As a result, the protein or its derivative can be synthesized by standard chemical methods known in the art (e.g., Hunkapiller et al., 1984, *Nature* 310:105-111).

Manipulations of component protein sequences may be made at the protein level. Included within the scope of the invention is a complex in which the component proteins or derivatives and analogs that are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease,  $\text{NaBH}_4$ , acetylation, formylation, oxidation, reduction, metabolic synthesis in the presence of tunicamycin, etc.

In specific embodiments, the amino acid sequences are modified to include a fluorescent label. In another specific embodiment, the protein sequences are modified to have a heterofunctional reagent; such heterofunctional reagents can be used to crosslink the members of the complex.

In addition, complexes of analogs and derivatives of component proteins can be chemically synthesized. For example, a peptide corresponding to a portion of a component protein, which comprises the desired domain or mediates the desired activity in vitro (e.g., complex formation) can be synthesized by use of a peptide synthesizer. Furthermore, if desired, non-classical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the protein sequence.

In cases where natural products are suspected of being mutant or are isolated from new species, the amino acid sequence of a component protein isolated from the natural source, as well as those expressed in vitro, or from synthesized expression vectors in vivo or in vitro, can be determined from analysis of the DNA sequence, or alternatively, by direct sequencing of the isolated protein. Such analysis can be performed by manual sequencing or through use of an automated amino acid sequenator.

The complexes can also be analyzed by hydrophilicity analysis (Hopp and Woods, 1981, Proc. Natl. Acad. Sci. USA 78:3824-3828). A hydrophilicity profile can be used to identify the hydrophobic and hydrophilic regions of the proteins, and help predict their orientation in designing substrates for experimental manipulation, such as in binding experiments, antibody synthesis, etc. Secondary structural analysis can also be done to identify regions of the component proteins, or their derivatives, that assume specific structures (Chou and Fasman, 1974, Biochemistry 13:222-23). Manipulation, translation, secondary structure prediction, hydrophilicity and hydrophobicity profile predictions, open reading frame prediction and plotting, and determination of sequence homologies, etc., can be accomplished using computer software programs available in the art.

Other methods of structural analysis including but not limited to X-ray crystallography (Engstrom, 1974, Biochem. Exp. Biol. 11:7-13), mass spectroscopy and gas chromatography (Methods in Protein Science, J. Wiley and Sons, New York, 1997), and computer modeling (Fletterick and Zoller, eds., 1986, Computer Graphics and Molecular Modeling, In: Current Communications in Molecular Biology, Cold Spring Harbor Laboratory, Cold Spring Harbor Press, New York) can also be employed.

#### **4.2 ANTIBODIES TO PROTEIN COMPLEXES/PROTEINS OF THE INVENTION**

According to the present invention, a protein complex of the present invention comprising a first protein, or a functionally active fragment or functionally active derivative thereof, selected from the group consisting of proteins listed in third column of table 1; and a second protein, or a functionally active fragment or functionally active derivative thereof, selected from the group consisting of proteins listed in fourth column of table 1, or a functionally active fragment or functionally active derivative thereof, can be used as an immunogen to generate antibodies which immunospecifically bind such immunogen. According to the present invention, also a protein complex of the present invention can be used as an immunogen to generate antibodies which immunospecifically bind to such immunogen comprising all proteins listed in fifth column of table 1.

Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, Fab fragments, and an Fab expression library. In a specific embodiment, antibodies to a complex comprising human protein components are

produced. In another embodiment, a complex formed from a fragment of said first protein and a fragment of said second protein, which fragments contain the protein domain that interacts with the other member of the complex, are used as an immunogen for antibody production. In a preferred embodiment, the antibody specific for the complex in that the antibody does not bind the individual protein components of the complex.

Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a polypeptide of the invention as an immunogen. Preferred polyclonal antibody compositions are ones that have been selected for antibodies directed against a polypeptide or polypeptides of the invention. Particularly preferred polyclonal antibody preparations are ones that contain only antibodies directed against a polypeptide or polypeptides of the invention. Particularly preferred immunogen compositions are those that contain no other human proteins such as, for example, immunogen compositions made using a non-human host cell for recombinant expression of a polypeptide of the invention. In such a manner, the only human epitope or epitopes recognized by the resulting antibody compositions raised against this immunogen will be present as part of a polypeptide or polypeptides of the invention.

The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If desired, the antibody molecules can be isolated from the mammal (e.g., from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction. Alternatively, antibodies specific for a protein or polypeptide of the invention can be selected for (e.g., partially purified) or purified by, e.g., affinity chromatography. For example, a recombinantly expressed and purified (or partially purified) protein of the invention is produced as described herein, and covalently or non-covalently coupled to a solid support such as, for example, a chromatography column. The column can then be used to affinity purify antibodies specific for the proteins of the invention from a sample containing antibodies directed against a large number of different epitopes, thereby generating a substantially purified antibody composition, i.e., one that is substantially free of contaminating antibodies. By a substantially purified antibody composition is meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those on the desired protein or polypeptide of the invention, and preferably at most 20%, yet more preferably at most 10%, and most preferably at

most 5% (by dry weight) of the sample is contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein or polypeptide of the invention.

At an appropriate time after immunization, e.g., when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein, 1975, *Nature* 256:495-497, the human B cell hybridoma technique (Kozbor et al., 1983, *Immunol. Today* 4:72), the EBV-hybridoma technique (Cole et al., 1985, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology* 1994, Coligan et al. (eds.) John Wiley & Sons, Inc., New York, NY). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, e.g., using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia Recombinant Phage Antibody System, Catalog No. 27-9400-01; and the Stratagene SurfZAP Phage Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs et al., 1991, *Bio/Technology* 9:1370-1372; Hay et al., 1992, *Hum. Antibod. Hybridomas* 3:81-85; Huse et al., 1989, *Science* 246:1275-1281; Griffiths et al., 1993, *EMBO J.* 12:725-734.

Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. A chimeric antibody is a molecule in which different portions are derived from different

animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, e.g., Cabilly et al., U.S. Patent No. 4,816,567; and Boss et al., U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Humanized antibodies are antibody molecules from non-human species having one or more complementarily determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule. (See, e.g., Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better et al., 1988, *Science* 240:1041-1043; Liu et al., 1987, *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu et al., 1987, *J. Immunol.* 139:3521-3526; Sun et al., 1987, *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura et al., 1987, *Canc. Res.* 47:999-1005; Wood et al., 1985, *Nature* 314:446-449; and Shaw et al., 1988, *J. Natl. Cancer Inst.* 80:1553-1559; Morrison, 1985, *Science* 229:1202-1207; Oi et al., 1986, *Bio/Techniques* 4:214; U.S. Patent 5,225,539; Jones et al., 1986, *Nature* 321:552-525; Verhoeyan et al., 1988, *Science* 239:1534; and Beidler et al., 1988, *J. Immunol.* 141:4053-4060.

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Such antibodies can be produced, for example, using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, 1995, *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In

addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., 1994, *Bio/technology* 12:899-903).

Antibody fragments that contain the idiotypes of the complex can be generated by techniques known in the art. For example, such fragments include, but are not limited to, the F(ab')<sub>2</sub> fragment which can be produced by pepsin digestion of the antibody molecule; the Fab' fragment that can be generated by reducing the disulfide bridges of the F(ab')<sub>2</sub> fragment; the Fab fragment that can be generated by treating the antibody molecular with papain and a reducing agent; and Fv fragments.

In the production of antibodies, screening for the desired antibody can be accomplished by techniques known in the art, e.g., ELISA (enzyme-linked immunosorbent assay). To select antibodies specific to a particular domain of the complex, or a derivative thereof, one may assay generated hybridomas for a product that binds to the fragment of the complex, or a derivative thereof, that contains such a domain. For selection of an antibody that specifically binds a complex of the present, or a derivative, or homologue thereof, but which does not specifically bind to the individual proteins of the complex, or a derivative, or homologue thereof, one can select on the basis of positive binding to the complex and a lack of binding to the individual protein components.

Antibodies specific to a domain of the complex, or a derivative, or homologue thereof, are also provided.

The foregoing antibodies can be used in methods known in the art relating to the localization and/or quantification of the complexes of the invention, e.g., for imaging these proteins, measuring levels thereof in appropriate physiological samples (by immunoassay), in diagnostic methods, etc. This hold true also for a derivative, or homologue thereof of a complex.

In another embodiment of the invention (see *infra*), an antibody to a complex or a fragment of such antibodies containing the antibody binding domain, is a therapeutic.

#### 4.3 DIAGNOSTIC, PROGNOSTIC, AND SCREENING USES OF THE PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

The particular protein complexes and proteins of the present invention may be markers of normal physiological processes, and thus have diagnostic utility. Further, definition of particular groups of patients with elevations or deficiencies of a protein complex of the present invention, or wherein the protein complex has a change in protein component composition, can lead to new nosological classifications of diseases, furthering diagnostic ability.

Examples for diseases or disorders are neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

Detecting levels of protein complexes, or individual component proteins that form the complexes, or detecting levels of the mRNAs encoding the components of the complex, may be used in diagnosis, prognosis, and/or staging to follow the course of a disease state, to follow a therapeutic response, etc.

A protein complex of the present invention and the individual components of the complex and a derivative, analog or subsequence thereof, encoding nucleic acids (and sequences complementary thereto), and anti-complex antibodies and antibodies directed against individual components that can form the complex, are useful in diagnostics. The foregoing molecules can be used in assays, such as immunoassays, to detect, prognose, diagnose, or monitor various conditions, diseases, and disorders characterized by aberrant levels of a complex or aberrant component composition of a complex, or monitor the treatment of such various conditions, diseases, and disorders.

In particular, such an immunoassay is carried out by a method comprising contacting a sample derived from a patient with an anti-complex antibody under conditions such that immunospecific binding can occur, and detecting or measuring the amount of any immunospecific binding by the antibody. In a specific aspect, such binding of antibody, in tissue sections, can be used to detect aberrant complex localization, or aberrant (e.g., high, low or absent) levels of a protein complex or complexes. In a specific embodiment, an antibody to the complex can be used to assay a patient tissue or serum sample for the presence of the complex, where an aberrant level of the complex is an indication of a diseased condition. By "aberrant levels" is meant increased or decreased levels relative to that present, or a standard level

representing that present, in an analogous sample from a portion or fluid of the body, or from a subject not having the disorder.

The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as Western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few known in the art.

Nucleic acids encoding the components of the protein complex and related nucleic acid sequences and subsequences, including complementary sequences, can be used in hybridization assays. The nucleic acid sequences, or subsequences thereof, comprising about at least 8 nucleotides, can be used as hybridization probes. Hybridization assays can be used to detect, prognose, diagnose, or monitor conditions, disorders, or disease states associated with aberrant levels of the mRNAs encoding the components of a complex as described, supra. In particular, such a hybridization assay is carried out by a method comprising contacting a sample containing nucleic acid with a nucleic acid probe capable of hybridizing to component protein coding DNA or RNA, under conditions such that hybridization can occur, and detecting or measuring any resulting hybridization.

In specific embodiments, diseases and disorders involving or characterized by aberrant levels of a protein complex or aberrant complex composition can be diagnosed, or its suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by determining the component protein composition of the complex, or detecting aberrant levels of a member of the complex or un-complexed component proteins or encoding nucleic acids, or functional activity including, but not restricted to, binding to an interacting partner, or by detecting mutations in component protein RNA, DNA or protein (e.g., mutations such as translocations, truncations, changes in nucleotide or amino acid sequence relative to wild-type that cause increased or decreased expression or activity of a complex, and/or component protein).

Such diseases and disorders include, but are not limited to neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

By way of example, levels of a protein complex and the individual components of a complex can be detected by immunoassay, levels of component protein RNA or DNA

can be detected by hybridization assays (e.g., Northern blots, dot blots, RNase protection assays), and binding of component proteins to each other (e.g., complex formation) can be measured by binding assays commonly known in the art. Translocations and point mutations in component protein genes can be detected by Southern blotting, RFLP analysis, PCR using primers that preferably generate a fragment spanning at least most of the gene by sequencing of genomic DNA or cDNA obtained from the patient, etc.

Assays well known in the art (e.g., assays described above such as immunoassays, nucleic acid hybridization assays, activity assays, etc.) can be used to determine whether one or more particular protein complexes are present at either increased or decreased levels, or are absent, in samples from patients suffering from a particular disease or disorder, or having a predisposition to develop such a disease or disorder, as compared to the levels in samples from subjects not having such a disease or disorder, or having a predisposition to develop such a disease or disorder. Additionally, these assays can be used to determine whether the ratio of the complex to the un-complexed components of the complex, is increased or decreased in samples from patients suffering from a particular disease or disorder, or having a predisposition to develop such a disease or disorder, as compared to the ratio in samples from subjects not having such a disease or disorder.

In the event that levels of one or more particular protein complexes (i.e., complexes formed from component protein derivatives, homologs, fragments, or analogs) are determined to be increased in patients suffering from a particular disease or disorder, or having a predisposition to develop such a disease or disorder, then the particular disease or disorder, or predisposition for a disease or disorder, can be diagnosed, have prognosis defined for, be screened for, or be monitored by detecting increased levels of the one or more protein complexes, increased levels of the mRNA that encodes one or more members of the one or more particular protein complexes, or by detecting increased complex functional activity.

Accordingly, in a specific embodiment of the present invention, diseases and disorders involving increased levels of one or more protein complexes can be diagnosed, or their suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by detecting increased levels of the one or more protein complexes, the mRNA encoding both members of the complex, or complex functional activity, or by detecting mutations in the component proteins that stabilize or enhance

complex formation, e.g., mutations such as translocations in nucleic acids, truncations in the gene or protein, changes in nucleotide or amino acid sequence relative to wild-type, that stabilize or enhance complex formation.

In the event that levels of one or more particular protein complexes are determined to be decreased in patients suffering from a particular disease or disorder, or having a predisposition to develop such a disease or disorder, then the particular disease or disorder or predisposition for a disease or disorder can be diagnosed, have its prognosis determined, be screened for, or be monitored by detecting decreased levels of the one or more protein complexes, the mRNA that encodes one or more members of the particular one or more protein complexes, or by detecting decreased protein complex functional activity.

Accordingly, in a specific embodiment of the invention, diseases and disorders involving decreased levels of one or more protein complexes can be diagnosed, or their suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by detecting decreased levels of the one or more protein complexes, the mRNA encoding one or more members of the one or more complexes, or complex functional activity, or by detecting mutations in the component proteins that decrease complex formation, e.g., mutations such as translocations in nucleic acids, truncations in the gene or protein, changes in nucleotide or amino acid sequence relative to wild-type, that decrease complex formation.

Accordingly, in a specific embodiment of the invention, diseases and disorders involving aberrant compositions of the complexes can be diagnosed, or their suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by detecting the component proteins of one or more complexes, or the mRNA encoding the members of the one or more complexes.

The use of detection techniques, especially those involving antibodies against a protein complex, provides a method of detecting specific cells that express the complex or component proteins. Using such assays, specific cell types can be defined in which one or more particular protein complexes are expressed, and the presence of the complex or component proteins can be correlated with cell viability, state, health, etc.

Also embodied are methods to detect a protein complex of the present invention in cell culture models that express particular protein complexes or derivatives thereof, for the purpose of characterizing or preparing the complexes for harvest. This embodiment includes cell sorting of prokaryotes such as but not restricted to bacteria (Davey and Kell,

1996, Microbiol. Rev. 60:641-696), primary cultures and tissue specimens from eukaryotes, including mammalian species such as human (Steele et al., 1996, Clin. Obstet. Gynecol 39:801-813), and continuous cell cultures (Orfao and Ruiz-Arguelles, 1996, Clin. Biochem. 29:5-9). Such isolations can be used as methods of diagnosis, described, supra.

In a further specific embodiment, a modulation of the formation process of a complex can be determined.

Such a modulation can either be a change in the typical time course of its formation or a change in the typical steps leading to the formation of the complete complex.

Such changes can for example be detected by analysing and comparing the process of complex formation in untreated wild type cells of a particular type and/or cells showing or having the predisposition to develop a certain disease phenotype and/or cells which have been treated with particular conditions and/or particular agents in a particular situation.

Methods to study such changes in time course are well known in the art and include for example Western-blot analysis of the proteins in the complex isolated at different steps of its formation.

Furthermore an aberrant intracellular localization of the protein complex and/or an aberrant transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or a gene dependent on the complex can serve as a marker for a disease and thus have diagnostic utility for any disease which is caused by an aberrant activity, function, composition or formation of the complex of the invention.

Methods to study the intracellular localization are well known in the art and include, but are not limited to immunofluorescence analysis using antibodies specific for components of the protein. Preferentially, double-stainings including staining of other cellular structures are being used to facilitate the detection of the intracellular localization. Methods to analyse the transcription levels of a gene dependent on the complex are also well known in the art and include Northern blot analysis, quantitative PCR etc. The abundance of proteins dependent on the protein can be analyzed as described supra. Methods to study changes in the activity of proteins dependent on complex depend on the protein. The choice of such methods will be apparent to any person skilled in the art.

#### 4.4 THERAPEUTIC USES OF PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

The present invention is directed to a method for treatment or prevention of various diseases and disorders by administration of a therapeutic compound. (termed herein "therapeutic"). Such "therapeutics" include, but are not limited to, a protein complex of the present invention, the individual component proteins, and analogs and derivatives (including fragments) of the foregoing (e.g., as described hereinabove); antibodies thereto (as described hereinabove); nucleic acids encoding the component protein, and analogs or derivatives, thereof (e.g., as described hereinabove); component protein antisense nucleic acids, and agents that modulate complex formation and/or activity (i.e., agonists and antagonists).

The protein complexes as identified herein can be implicated in processes which are implicated in or associated with pathological conditions. Diseases and disorders which can be treated and/or prevented and/or diagnosed by therapeutics interacting with any of the complexes provided herein are for example neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders, inflammatory diseases such as chronic inflammatory disorders, rheumatoid arthritis and inflammatory bowel disease.

These disorders are treated or prevented by administration of a therapeutic that modulates (i.e. inhibits or promotes) protein complex activity or formation or modulates its function or composition. Diseases or disorders associated with aberrant levels of complex activity or formation, or aberrant levels or activity of the component proteins, or aberrant complex composition or a change in the function, may be treated by administration of a therapeutic that modulates complex formation or activity or by the administration of a protein complex.

Therapeutics may also be administered to modulate complex formation or activity or level thereof in a microbial organism such as yeast, fungi such as candida albicans causing an infectious disease in animals or humans.

Diseases and disorders characterized by increased (relative to a subject not suffering from the disease or disorder) complex levels or activity can be treated with therapeutics that antagonize (i.e., reduce or inhibit) complex formation or activity. Therapeutics that can be used include, but are not limited to, the component proteins or

an analog, derivative or fragment of the component protein; anti-complex antibodies (e.g., antibodies specific for the protein complex, or a fragment or derivative of the antibody containing the binding region thereof; nucleic acids encoding the component proteins; antisense nucleic acids complementary to nucleic acids encoding the component proteins; and nucleic acids encoding the component protein that are dysfunctional due to, e.g., a heterologous insertion within the protein coding sequence, that are used to "knockout" endogenous protein function by homologous recombination, see, e.g., Capecchi, 1989, *Science* 244:1288-1292. In one embodiment, a therapeutic is 1, 2 or more antisense nucleic acids which are complementary to 1, 2, or more nucleic acids, respectfully, that encode component proteins of a complex.

In a specific embodiment of the present invention, a nucleic acid containing a portion of a component protein gene in which gene sequences flank (are both 5' and 3' to) a different gene sequence, is used as a component protein antagonist, or to promote component protein inactivation by homologous recombination (see also, Koller and Smithies, 1989, *Proc. Natl. Acad. Sci. USA* 86:8932-8935; Zijlstra et al., 1989, *Nature* 342: 435-438). Additionally, mutants or derivatives of a component protein that has greater affinity for another component protein or the complex than wild type may be administered to compete with wild type protein for binding, thereby reducing the levels of complexes containing the wild type protein. Other therapeutics that inhibit complex function can be identified by use of known convenient in vitro assays, e.g., based on their ability to inhibit complex formation, or as described in Section 4.5, *infra*.

In specific embodiments, therapeutics that antagonize complex formation or activity are administered therapeutically, including prophylactically, (1) in diseases or disorders involving an increased (relative to normal or desired) level of a complex, for example, in patients where complexes are overactive or overexpressed; or (2) in diseases or disorders where an in vitro (or in vivo) assay (see *infra*) indicates the utility of antagonist administration. Increased levels of a complex can be readily detected, e.g., by quantifying protein and/or RNA, by obtaining a patient tissue sample (e.g., from biopsy tissue) and assaying it in vitro for RNA or protein levels, or structure and/or activity of the expressed complex (or the encoding mRNA). Many methods standard in the art can be thus employed including, but not limited to, immunoassays to detect complexes and/or visualize complexes (e.g., Western blot analysis, immunoprecipitation followed by sodium dodecyl sulfate polyacrylamide gel electrophoresis [SDS-PAGE], immunocytochemistry, etc.), and/or hybridization assays to detect concurrent expression

of component protein mRNA (e.g., Northern assays, dot blot analysis, in situ hybridization, etc.).

A more specific embodiment of the present invention is directed to a method of reducing complex expression (i.e., expression of the protein components of the complex and/or formation of the complex) by targeting mRNAs that express the protein moieties. RNA therapeutics currently fall within three classes, antisense species, ribozymes, or RNA aptamers (Good et al., 1997, *Gene Therapy* 4:45-54).

Antisense oligonucleotides have been the most widely used. By way of example, but not limitation, antisense oligonucleotide methodology to reduce complex formation is presented below, *infra*. Ribozyme therapy involves the administration, induced expression, etc. of small RNA molecules with enzymatic ability to cleave, bind, or otherwise inactivate specific RNAs, to reduce or eliminate expression of particular proteins (Grassi and Marini, 1996, *Annals of Medicine* 28:499-510; Gibson, 1996, *Cancer and Metastasis Reviews* 15:287-299). RNA aptamers are specific RNA ligand proteins, such as for Tat and Rev RNA (Good et al., 1997, *Gene Therapy* 4:45-54) that can specifically inhibit their translation. Aptamers specific for component proteins can be identified by many methods well known in the art, for example, by affecting the formation of a complex in the protein-protein interaction assay described, *infra*.

In another embodiment, the activity or levels of a component protein are reduced by administration of another component protein, or the encoding nucleic acid, or an antibody that immunospecifically binds to the component protein, or a fragment or a derivative of the antibody containing the binding domain thereof.

In another aspect of the invention, diseases or disorders associated with increased levels of an component protein of the complex may be treated or prevented by administration of a therapeutic that increases complex formation if the complex formation acts to reduce or inactivate the component protein through complex formation. Such diseases or disorders can be treated or prevented by administration of one component member of the complex, administration of antibodies or other molecules that stabilize the complex, etc.

Diseases and disorders associated with underexpression of a complex, or a component protein, are treated or prevented by administration of a therapeutic that promotes (i.e., increases or supplies) complex levels and/or function, or individual component protein function. Examples of such a therapeutic include but are not limited to a complex or a derivative, analog or fragment of the complex that are functionally

active (e.g., able to form a complex), un-complexed component proteins and derivatives, analogs, and fragments of un-complexed component proteins, and nucleic acids encoding the members of a complex or functionally active derivatives or fragments of the members of the complex, e.g., for use in gene therapy. In a specific embodiment, a therapeutic includes derivatives, homologs or fragments of a component protein that increase and/or stabilize complex formation. Examples of other agonists can be identified using in vitro assays or animal models, examples of which are described, *infra*.

In yet other specific embodiments of the present invention, therapeutics that promote complex function are administered therapeutically, including prophylactically, (1) in diseases or disorders involving an absence or decreased (relative to normal or desired) level of a complex, for example, in patients where a complex, or the individual components necessary to form the complex, is lacking, genetically defective, biologically inactive or underactive, or under-expressed; or (2) in diseases or disorders wherein an in vitro or in vivo assay (see, *infra*) indicates the utility of complex agonist administration. The absence or decreased level of a complex, component protein or function can be readily detected, e.g., by obtaining a patient tissue sample (e.g., from biopsy tissue) and assaying it in vitro for RNA or protein levels, structure and/or activity of the expressed complex and/or the concurrent expression of mRNA encoding the two components of the complex. Many methods standard in the art can be thus employed, including but not limited to immunoassays to detect and/or visualize a complex, or the individual components of a complex (e.g., Western blot analysis, immunoprecipitation followed by sodium dodecyl sulfate polyacrylamide gel electrophoresis [SDS-PAGE], immunocytochemistry, etc.) and/or hybridization assays to detect expression of mRNAs encoding the individual protein components of a complex by detecting and/or visualizing component mRNA concurrently or separately using, e.g., Northern assays, dot blot analysis, in situ hybridization, etc.

In specific embodiments, the activity or levels of a component protein are increased by administration of another component protein of the same complex, or a derivative, homolog or analog thereof, a nucleic acid encoding the other component, or an agent that stabilizes or enhances the other component, or a fragment or derivative of such an agent.

Generally, administration of products of species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, a human complex, or derivative, homolog or analog thereof;

nucleic acids encoding the members of the human complex or a derivative, homolog or analog thereof; an antibody to a human complex, or a derivative thereof; or other human agents that affect component proteins or the complex, are therapeutically or prophylactically administered to a human patient.

Preferably, suitable in vitro or in vivo assays are utilized to determine the effect of a specific therapeutic and whether its administration is indicated for treatment of the affected tissue or individual.

In various specific embodiments, in vitro assays can be carried out with representative cells of cell types involved in a patient's disorder, to determine if a therapeutic has a desired effect upon such cell types.

Compounds for use in therapy can be tested in suitable animal model systems prior to testing in humans, including, but not limited to, rats, mice, chicken, cows, monkeys, rabbits, etc. For in vivo testing, prior to administration to humans, any animal model system known in the art may be used. Additional descriptions and sources of therapeutics that can be used according to the invention are found in Sections 4.1 to 4.3 and 4.7 herein.

#### 4.4.1 GENE THERAPY

In a specific embodiment of the present invention, nucleic acids comprising a sequence encoding the component proteins, or a functional derivative thereof, are administered to modulate complex activity or formation by way of gene therapy. Gene therapy refers to therapy performed by the administration of a nucleic acid to a subject. In this embodiment of the present invention, the nucleic acid expresses its encoded protein(s) that mediates a therapeutic effect by modulating complex activity or formation. Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., 1993, *Clinical Pharmacy* 12:488-505; Wu and Wu, 1991, *Biotherapy* 3:87-95; Tolstoshev, 1993, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596; Mulligan, 1993, *Science* 260:926-932; Morgan and Anderson, 1993, *Ann. Rev. Biochem.* 62:191-217; and May, 1993, *TIBTECH* 11:155-215. Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al., eds., 1993, *Current Protocols in Molecular*

Biology, John Wiley & Sons, NY; and Kriegler, 1990, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY.

In a preferred aspect, the therapeutic comprises a nucleic acid that is part of an expression vector that expresses one or more of the component proteins, or fragments or chimeric proteins thereof, in a suitable host. In particular, such a nucleic acid has a promoter operably linked to the protein coding region(s) (or, less preferably separate promoters linked to the separate coding regions separately), said promoter being inducible or constitutive, and optionally, tissue-specific. In another particular embodiment, a nucleic acid molecule is used in which the coding sequences, and any other desired sequences, are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intra-chromosomal expression of the component protein nucleic acids (Koller and Smithies, 1989, Proc. Natl. Acad. Sci. USA 86:8932-8935; Zijlstra et al., 1989, Nature 342:435-438).

Delivery of the nucleic acid into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid-carrying vector, or indirect, in which case, cells are first transformed with the nucleic acid in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

In a specific embodiment, the nucleic acid is directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by infection using a defective or attenuated retroviral or other viral vector (U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors, or through use of transfecting agents, by encapsulation in liposomes, microparticles, or microcapsules, or by administering it in linkage to a peptide that is known to enter the nucleus, or by administering it in linkage to a ligand subject to receptor-mediated endocytosis that can be used to target cell types specifically expressing the receptors (e.g., Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432), etc. In another embodiment, a nucleic acid-ligand complex can be formed in which the ligand comprises a fusogenic viral peptide that disrupts endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor

(see, e.g., International Patent Publications WO 92/06180; WO 92/22635; WO 92/20316; WO 93/14188; and WO 93/20221. Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, 1989, *Proc. Natl. Acad. Sci. USA* 86:8932-8935; Zijlstra et al., 1989, *Nature* 342:435-438).

In a specific embodiment, a viral vector that contains the component protein encoding nucleic acids is used. For example, a retroviral vector can be used (Miller et al., 1993, *Meth. Enzymol.* 217:581-599). These retroviral vectors have been modified to delete retroviral sequences that are not necessary for packaging of the viral genome and integration into host cell DNA. The encoding nucleic acids to be used in gene therapy is/are cloned into the vector, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., 1994, *Biotherapy* 6:291-302, which describes the use of a retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are Clowes et al., 1994, *J. Clin. Invest.* 93:644-651; Kiem et al., 1994, *Blood* 83:1467-1473; Salmons and Gunzberg, 1993, *Human Gene Therapy* 4:129-141; and Grossman and Wilson, 1993, *Curr. Opin. in Genetics and Devel.* 3:110-114.

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are the liver, the central nervous system, endothelial cells and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, 1993, *Curr. Opin. Genet. Devel.* 3:499-503, discuss adenovirus-based gene therapy. The use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys has been demonstrated by Bout et al., 1994, *Human Gene Therapy* 5:3-10. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., 1991, *Science* 252:431-434; Rosenfeld et al., 1992, *Cell* 68:143-155; and Mastrangeli et al., 1993, *J. Clin. Invest.* 91:225-234.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., 1993, *Proc. Soc. Exp. Biol. Med.* 204:289-300).

Another approach to gene therapy involves transferring a gene into cells in tissue culture by methods such as electroporation, lipofection, calcium phosphate-mediated

transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene from those that have not. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art including, but not limited to, transfection by electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, 1993, *Meth. Enzymol.* 217:599-618; Cohen et al., 1993, *Meth. Enzymol.* 217:618-644; Cline, 1985, *Pharmac. Ther.* 29:69-92) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably, is heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. In a preferred embodiment, epithelial cells are injected, e.g., subcutaneously. In another embodiment, recombinant skin cells may be applied as a skin graft onto the patient. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes, blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, and granulocytes, various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, a component protein encoding nucleic acid is/are introduced into the cells such that the gene or genes are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention. Such stem cells include but are not limited to hematopoietic stem cells (HSCs), stem cells of epithelial tissues such as the skin and the lining of the gut, embryonic heart muscle cells, liver stem cells (International Patent Publication WO 94/08598), and neural stem cells (Stemple and Anderson, 1992, Cell 71:973-985).

Epithelial stem cells (ESCs), or keratinocytes, can be obtained from tissues such as the skin and the lining of the gut by known procedures (Rheinwald, 1980, Meth. Cell Biol. 2A:229). In stratified epithelial tissue such as the skin, renewal occurs by mitosis of stem cells within the germinal layer, the layer closest to the basal lamina. Similarly, stem cells within the lining of the gut provide for a rapid renewal rate of this tissue. ESCs or keratinocytes obtained from the skin or lining of the gut of a patient or donor can be grown in tissue culture (Rheinwald, 1980, Meth. Cell Bio. 2A:229; Pittelkow and Scott, 1986, Mayo Clinic Proc. 61:771). If the ESCs are provided by a donor, a method for suppression of host versus graft reactivity (e.g., irradiation, or drug or antibody administration to promote moderate immunosuppression) can also be used.

With respect to hematopoietic stem cells (HSCs), any technique that provides for the isolation, propagation, and maintenance in vitro of HSCs can be used in this embodiment of the invention. Techniques by which this may be accomplished include (a) the isolation and establishment of HSC cultures from bone marrow cells isolated from the future host, or a donor, or (b) the use of previously established long-term HSC cultures, which may be allogeneic or xenogeneic. Non-autologous HSCs are used preferably in conjunction with a method of suppressing transplantation immune reactions between the future host and patient. In a particular embodiment of the present invention, human bone marrow cells can be obtained from the posterior iliac crest by needle aspiration (see, e.g., Kodo et al., 1984, J. Clin. Invest. 73: 1377-1384). In a preferred embodiment of the present invention, the HSCs can be made highly enriched or in substantially pure form. This enrichment can be accomplished before, during, or after long-term culturing, and can be done by any technique known in the art. Long-term cultures of bone marrow cells can be established and maintained by using, for example,

modified Dexter cell culture techniques (Dexter et al., 1977, J. Cell Physiol. 91:335) or Witlock-Witte culture techniques (Witlock and Witte, 1982, Proc. Natl. Acad. Sci. USA 79:3608-3612).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

Additional methods can be adapted for use to deliver a nucleic acid encoding the component proteins, or functional derivatives thereof, e.g., as described in Section 4.1, supra.

#### 4.4.2 USE OF ANTISENSE OLIGONUCLEOTIDES FOR SUPPRESSION OF PROTEIN COMPLEX FORMATION OR PROTEIN COMPLEX/PROTEIN ACTIVITY

In a specific embodiment of the present invention, protein complex activity and formation and protein activity is inhibited by use of antisense nucleic acids for the component proteins of the complex, that inhibit transcription and/or translation of their complementary sequence. The present invention provides the therapeutic or prophylactic use of nucleic acids of at least six nucleotides that are antisense to a gene or cDNA encoding a component protein, or a portion thereof. An "antisense" nucleic acid as used herein refers to a nucleic acid capable of hybridizing to a sequence-specific portion of a component protein RNA (preferably mRNA) by virtue of some sequence complementarity. The antisense nucleic acid may be complementary to a coding and/or noncoding region of a component protein mRNA. Such antisense nucleic acids that inhibit complex formation or activity have utility as therapeutics, and can be used in the treatment or prevention of disorders as described supra.

The antisense nucleic acids of the invention can be oligonucleotides that are double-stranded or single-stranded, RNA or DNA, or a modification or derivative thereof, which can be directly administered to a cell, or which can be produced intracellularly by transcription of exogenous, introduced sequences.

In another embodiment, the present invention is directed to a method for inhibiting the expression of component protein nucleic acid sequences, in a prokaryotic or eukaryotic cell, comprising providing the cell with an effective amount of a composition

comprising an antisense nucleic acid of the component protein, or a derivative thereof, of the invention.

The antisense nucleic acids are of at least six nucleotides and are preferably oligonucleotides, ranging from 6 to about 200 nucleotides. In specific aspects, the oligonucleotide is at least 10 nucleotides, at least 15 nucleotides, at least 100 nucleotides, or at least 200 nucleotides. The oligonucleotides can be DNA or RNA or chimeric mixtures, or derivatives or modified versions thereof, and either single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone. The oligonucleotide may include other appending groups such as peptides, agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. USA 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. USA 84:648-652; International Patent Publication No. WO 88/09810) or blood-brain barrier (see, e.g., International Patent Publication No. WO 89/10134), hybridization-triggered cleavage agents (see, e.g., Krol et al., 1988, BioTechniques 6:958-976), or intercalating agents (see, e.g., Zon, 1988, Pharm. Res. 5:539-549).

In a preferred aspect of the invention, an antisense oligonucleotide is provided, preferably as single-stranded DNA. The oligonucleotide may be modified at any position in its structure with constituents generally known in the art.

The antisense oligonucleotides may comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl)uracil, 5-carboxymethylaminomethyl-2-thio-uridine, 5-carboxymethylaminomethyluracil, dihydrouracil,  $\beta$ -D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil,  $\beta$ -D-mannosylqueosine, 5N-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methyl-thio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

In another embodiment, the oligonucleotide comprises at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the oligonucleotide comprises at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal, or an analog of the foregoing.

In yet another embodiment, the oligonucleotide is a 2'-anomeric oligonucleotide. An  $\alpha$ -anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual  $\beta$ -units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641).

The oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization-triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

Oligonucleotides of the invention may be synthesized by standard methods known in the art, e.g., by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligo-nucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. USA 85:7448-7451), etc.

In a specific embodiment, the antisense oligonucleotides comprise catalytic RNAs, or ribozymes (see, e.g., International Patent Publication No. WO 90/11364; Sarver et al., 1990, Science 247:1222-1225). In another embodiment, the oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analog (Inoue et al., 1987, FEBS Lett. 215:327-330).

In an alternative embodiment, the antisense nucleic acids of the invention are produced intracellularly by transcription from an exogenous sequence. For example, a vector can be introduced in vivo such that it is taken up by a cell, within which cell the vector or a portion thereof is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the component protein. Such a vector can remain episomal or become chromosomally integrated, as long as it

can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art to be capable of replication and expression in mammalian cells. Expression of the sequences encoding the antisense RNAs can be by any promoter known in the art to act in mammalian, preferably human, cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, 1981, *Nature* 290:304-310), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., 1980, *Cell* 22:787-797), the herpes thymidine kinase promoter (Wagner et al., 1981, *Proc. Natl. Acad. Sci. USA* 78:1441-1445), the regulatory sequences of the metallothionein gene (Brinster et al., 1982, *Nature* 296:39-42), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a component protein gene, preferably a human gene. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," as referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the longer the hybridizing nucleic acid, the more base mismatches with a component protein RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

The component protein antisense nucleic acids can be used to treat (or prevent) disorders of a cell type that expresses, or preferably overexpresses, a protein complex.

Cell types that express or overexpress component protein RNA can be identified by various methods known in the art. Such methods include, but are not limited to, hybridization with component protein-specific nucleic acids (e.g., by Northern blot hybridization, dot blot hybridization, or in situ hybridization), or by observing the ability of RNA from the cell type to be translated in vitro into the component protein by immunohistochemistry, Western blot analysis, ELISA, etc. In a preferred aspect, primary tissue from a patient can be assayed for protein expression prior to treatment, e.g., by

immunocytochemistry, in situ hybridization, or any number of methods to detect protein or mRNA expression.

Pharmaceutical compositions of the invention (see Section 4.7, *infra*), comprising an effective amount of a protein component antisense nucleic acid in a pharmaceutically acceptable carrier can be administered to a patient having a disease or disorder that is of a type that expresses or overexpresses a protein complex of the present invention.

The amount of antisense nucleic acid that will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. Where possible, it is desirable to determine the antisense cytotoxicity *in vitro*, and then in useful animal model systems, prior to testing and use in humans.

In a specific embodiment, pharmaceutical compositions comprising antisense nucleic acids are administered via liposomes, microparticles, or microcapsules. In various embodiments of the invention, it may be useful to use such compositions to achieve sustained release of the antisense nucleic acids. In a specific embodiment, it may be desirable to utilize liposomes targeted via antibodies to specific identifiable central nervous system cell types (Leonetti et al., 1990, *Proc. Natl. Acad. Sci. U.S.A.* 87:2448-2451; Renneisen et al., 1990, *J. Biol. Chem.* 265:16337-16342).

#### 4.5 ASSAYS OF PROTEIN COMPLEXES/PROTEINS OF THE INVENTION AND DERIVATIVES AND ANALOGS THEREOF

The functional activity of a protein complex of the present invention, or a derivative, fragment or analog thereof or protein component thereof, can be assayed by various methods. Potential modulators (e.g., agonists and antagonists) of complex activity or formation, e.g., anti-complex antibodies and antisense nucleic acids, can be assayed for the ability to modulate complex activity or formation.

In one embodiment of the present invention, where one is assaying for the ability to bind or compete with a wild-type complex for binding to an anti-complex antibody, various immunoassays known in the art can be used, including but not limited to competitive and non-competitive assay systems using techniques such as radioimmunoassay, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitin reactions,

immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels), western blot analysis, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

The expression of the component protein genes (both endogenous and those expressed from cloned DNA containing the genes) can be detected using techniques known in the art, including but not limited to Southern hybridization (Southern, 1975, J. Mol. Biol. 98:503-517), northern hybridization (see, e.g., Freeman et al., 1983, Proc. Natl. Acad. Sci. USA 80:4094-4098), restriction endonuclease mapping (Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, 2<sup>nd</sup> Ed. Cold Spring Harbor Laboratory Press, New York), RNase protection assays (Current Protocols in Molecular Biology, John Wiley and Sons, New York, 1997), DNA sequence analysis, and polymerase chain reaction amplification (PCR; U.S. Patent Nos. 4,683,202, 4,683,195, and 4,889,818; Gyllenstein et al., 1988, Proc. Natl. Acad. Sci. USA 85:7652-7657; Ochman et al., 1988, Genetics 120:621-623; Loh et al., 1989, Science 243:217-220) followed by Southern hybridization with probes specific for the component protein genes, in various cell types. Methods of amplification other than PCR commonly known in the art can be employed. In one embodiment, Southern hybridization can be used to detect genetic linkage of component protein gene mutations to physiological or pathological states. Various cell types, at various stages of development, can be characterized for their expression of component proteins at the same time and in the same cells. The stringency of the hybridization conditions for northern or Southern blot analysis can be manipulated to ensure detection of nucleic acids with the desired degree of relatedness to the specific probes used. Modifications to these methods and other methods commonly known in the art can be used.

Derivatives (e.g., fragments), homologs and analogs of one component protein can be assayed for binding to another component protein in the same complex by any method known in the art, for example the modified yeast matrix mating test described in Section 4.6.1 *infra*, immunoprecipitation with an antibody that binds to the component

protein complexed with other component proteins in the same complex, followed by size fractionation of the immunoprecipitated proteins (e.g., by denaturing or nondenaturing polyacrylamide gel electrophoresis), Western blot analysis, etc.

One embodiment of the invention provides a method for screening a derivative, homolog or analog of a component protein for biological activity comprising contacting said derivative, homolog or analog of the component protein with the other component proteins in the same complex; and detecting the formation of a complex between said derivative, homolog or analog of the component protein and the other component proteins; wherein detecting formation of said complex indicates that said derivative, homolog or analog of has biological (e.g., binding) activity.

The invention also provides methods of modulating the activity of a component protein that can participate in a protein complex by administration of a binding partner of that protein or derivative, homolog or analog thereof.

In a specific embodiment of the present invention, a protein complex of the present invention is administered to treat or prevent a disease or disorder, since the complex and/or component proteins have been implicated in the disease and disorder. Accordingly, a protein complex or a derivative, homolog, analog or fragment thereof, nucleic acids encoding the component proteins, anti-complex antibodies, and other modulators of protein complex activity, can be tested for activity in treating or preventing a disease or disorder in in vitro and in vivo assays.

In one embodiment, a therapeutic of the invention can be assayed for activity in treating or preventing a disease by contacting cultured cells that exhibit an indicator of the disease in vitro, with the therapeutic, and comparing the level of said indicator in the cells contacted with the therapeutic, with said level of said indicator in cells not so contacted, wherein a lower level in said contacted cells indicates that the therapeutic has activity in treating or preventing the disease.

In another embodiment of the invention, a therapeutic of the invention can be assayed for activity in treating or preventing a disease by administering the therapeutic to a test animal that is predisposed to develop symptoms of a disease, and measuring the change in said symptoms of the disease after administration of said therapeutic, wherein a reduction in the severity of the symptoms of the disease or prevention of the symptoms of the disease indicates that the therapeutic has activity in treating or preventing the disease. Such a test animal can be any one of a number of animal models known in the art for disease. These animal models are well known in the art. These animal models

include, but are not limited to those which are listed in the section 4.6 (supra) as exemplary animal models to study any of the complexes provided in the invention.

#### **4.6 SCREENING FOR MODULATORS OF THE PROTEIN COMPLEXES/PROTEINS OF THE INVENTION**

A complex of the present invention, the component proteins of the complex and nucleic acids encoding the component proteins, as well as derivatives and fragments of the amino and nucleic acids, can be used to screen for compounds that bind to, or modulate the amount of, activity of, or protein component composition of, said complex, and thus, have potential use as modulators, i.e., agonists or antagonists, of complex activity, and/or complex formation, i.e., the amount of complex formed, and/or protein component composition of the complex.

Thus, the present invention is also directed to methods for screening for molecules that bind to, or modulate the function of, amount of, activity of, formation of or protein component composition of, a complex of the present invention. In one embodiment of the invention, the method for screening for a molecule that modulates directly or indirectly the function, activity or formation of a complex of the present invention comprises exposing said complex, or a cell or organism containing the complex machinery, to one or more candidate molecules under conditions conducive to modulation; and determining the amount of, the biochemical activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

In a further specific embodiment, a modulation of the formation process of a complex can be determined.

Such a modulation can either be a change in the typical time course of its formation or a change in the typical steps leading to the formation of the complete complex.

Such changes can for example be detected by analysing and comparing the process of complex formation in untreated wild type cells of a particular type and/or cells showing or having the predisposition to develop a certain disease phenotype and/or cells which have been treated with particular conditions and/or particular agents in a particular situation.

Methods to study such changes in time course are well known in the art and include for example Western-blot analysis of the proteins in the complex isolated at different steps of its formation.

Furthermore an aberrant intracellular localization of the protein complex and/or an aberrant transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or a gene dependent on the complex can serve as a marker for a disease and thus have diagnostic utility for any disease which is caused by an aberrant activity, function, composition or formation of the complex of the invention.

Methods to study the intracellular localization are well known in the art and include, but are not limited to immunofluorescence analysis using antibodies specific for components of the protein. Preferentially, double-stainings including staining of other cellular structures are being used to facilitate the detection of the intracellular localization. Methods to analyse the transcription levels of a gene dependent on the complex are also well known in the art and include Northern blot analysis, quantitative PCR etc. The abundance of proteins dependent on the protein can be analyzed as described supra. Methods to study changes in the activity of proteins dependent on complex depend on the protein. The choice of such methods will be apparent to any person skilled in the art.

In another embodiment, the present invention further relates to a process for the identification and/or preparation of an effector of the complex comprising the step of bringing into contact a product of any of claims 1 to 8 with a compound, a mixture or a library of compounds and determining whether the compound or a certain compound of the mixture or library binds to the product and/or effects the products biological activity and optionally further purifying the compound positively tested as effector.

In another embodiment, the present invention is directed to a method for screening for a molecule that binds a protein complex of the present invention comprising exposing said complex, or a cell or organism containing the complex machinery, to one or more candidate molecules; and determining whether said complex is bound by any of said candidate molecules. Such screening assays can be carried out using cell-free and cell-based methods that are commonly known in the art *in vitro*, *in vivo* or *ex vivo*. For example, an isolated complex can be employed, or a cell can be contacted with the candidate molecule and the complex can be isolated from such contacted cells and the isolated complex can be assayed for activity or component composition. In another example, a cell containing the complex can be contacted with the candidate molecule and the levels of the complex in the contacted cell can be measured. Additionally, such assays can be carried out in cells recombinantly expressing a component protein from the third column of table 1, or a functionally active fragment or functionally active derivative thereof, and a component protein from fourth column of table 1, or a functionally active fragment or functionally active derivative thereof. Additionally, such assays can also be carried out in cells recombinantly expressing all component proteins from the group of proteins in the fifth column of table 1.

For example, assays can be carried out using recombinant cells expressing the protein components of a complex, to screen for molecules that bind to, or interfere with, or promote complex activity or formation. In preferred embodiments, polypeptide derivatives that have superior stabilities but retain the ability to form a complex (e.g., one or more component proteins modified to be resistant to proteolytic degradation in the binding assay buffers, or to be resistant to oxidative degradation), are used to screen for modulators of complex activity or formation. Such resistant molecules can be generated, e.g., by substitution of amino acids at proteolytic cleavage sites, the use of chemically derivatized amino acids at proteolytic susceptible sites, and the replacement of amino acid residues subject to oxidation, i.e. methionine and cysteine.

A particular aspect of the present invention relates to identifying molecules that inhibit or promote formation or degradation of a complex of the present invention, e.g., using the method described for isolating the complex and identifying members of the complex using the TAP assay described in Section 4, *infra*, and in WO 00/09716 and Rigaut et al., 1999, *Nature Biotechnol.* 17:1030-1032, which are each incorporated by reference in their entirety. TNRF1

In another embodiment of the invention, a modulator is identified by administering a candidate molecule to a transgenic non-human animal expressing the complex component proteins from promoters that are not the native promoters of the respective proteins, more preferably where the candidate molecule is also recombinantly expressed in the transgenic non-human animal. Alternatively, the method for identifying such a modulator can be carried out *in vitro*, preferably with a purified complex, and a purified candidate molecule.

Agents/molecules (candidate molecules) to be screened can be provided as mixtures of a limited number of specified compounds, or as compound libraries, peptide libraries and the like. Agents/molecules to be screened may also include all forms of antisera, antisense nucleic acids, etc.; that can modulate complex activity or formation. Exemplary candidate molecules and libraries for screening are set forth in Section 4.6.1, *infra*.

Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, *Adv. Exp. Med. Biol.* 251:215-218; Scott and Smith, 1990, *Science* 249:386-390; Fowlkes et al., 1992, *BioTechniques* 13:422-427; Oldenburg et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:5393-5397; Yu et al., 1994, *Cell* 76:933-945; Staudt et al., 1988, *Science* 241:577-580; Bock et al., 1992, *Nature* 355:564-566; Tuerk et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:6988-6992; Ellington et al., 1992, *Nature* 355:850-852; U.S. Patent No. 5,096,815, U.S. Patent No. 5,223,409, and U.S. Patent No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, *Science* 263:671-673; and International Patent Publication No. WO 94/18318.

In a specific embodiment, screening can be carried out by contacting the library members with a complex immobilized on a solid phase, and harvesting those library members that bind to the protein (or encoding nucleic acid or derivative). Examples of such screening methods, termed "panning" techniques, are described by way of example in Parmley and Smith, 1988, *Gene* 73:305-318; Fowlkes et al., 1992, *BioTechniques* 13:422-427; International Patent Publication No. WO 94/18318; and in references cited hereinabove.

In a specific embodiment, fragments and/or analogs of protein components of a complex, especially peptidomimetics, are screened for activity as competitive or non-competitive inhibitors of complex formation (amount of complex or composition of

complex) or activity in the cell, which thereby inhibit complex activity or formation in the cell.

In one embodiment, agents that modulate (i.e., antagonize or agonize) complex activity or formation can be screened for using a binding inhibition assay, wherein agents are screened for their ability to modulate formation of a complex under aqueous, or physiological, binding conditions in which complex formation occurs in the absence of the agent to be tested. Agents that interfere with the formation of complexes of the invention are identified as antagonists of complex formation. Agents that promote the formation of complexes are identified as agonists of complex formation. Agents that completely block the formation of complexes are identified as inhibitors of complex formation.

Methods for screening may involve labeling the component proteins of the complex with radioligands (e.g.,  $^{125}\text{I}$  or  $^3\text{H}$ ), magnetic ligands (e.g., paramagnetic beads covalently attached to photobiotin acetate), fluorescent ligands (e.g., fluorescein or rhodamine), or enzyme ligands (e.g., luciferase or  $\beta$ -galactosidase). The reactants that bind in solution can then be isolated by one of many techniques known in the art, including but not restricted to, co-immunoprecipitation of the labeled complex moiety using antisera against the unlabeled binding partner (or labeled binding partner with a distinguishable marker from that used on the second labeled complex moiety), immunoaffinity chromatography, size exclusion chromatography, and gradient density centrifugation. In a preferred embodiment, the labeled binding partner is a small fragment or peptidomimetic that is not retained by a commercially available filter. Upon binding, the labeled species is then unable to pass through the filter, providing for a simple assay of complex formation.

Methods commonly known in the art are used to label at least one of the component members of the complex. Suitable labeling methods include, but are not limited to, radiolabeling by incorporation of radiolabeled amino acids, e.g.,  $^3\text{H}$ -leucine or  $^{35}\text{S}$ -methionine, radiolabeling by post-translational iodination with  $^{125}\text{I}$  or  $^{131}\text{I}$  using the chloramine T method, Bolton-Hunter reagents, etc., or labeling with  $^{32}\text{P}$  using phosphorylase and inorganic radiolabeled phosphorous, biotin labeling with photobiotin-acetate and sunlamp exposure, etc. In cases where one of the members of the complex is immobilized, e.g., as described infra, the free species is labeled. Where neither of the interacting species is immobilized, each can be labeled with a distinguishable marker such that isolation of both moieties can be followed to provide for more accurate quantification, and to distinguish the formation of homomeric from heteromeric

complexes. Methods that utilize accessory proteins that bind to one of the modified interactants to improve the sensitivity of detection, increase the stability of the complex, etc., are provided.

Typical binding conditions are, for example, but not by way of limitation, in an aqueous salt solution of 10-250 mM NaCl, 5-50 mM Tris-HCl, pH 5-8, and 0.5% Triton X-100 or other detergent that improves specificity of interaction. Metal chelators and/or divalent cations may be added to improve binding and/or reduce proteolysis. Reaction temperatures may include 4, 10, 15, 22, 25, 35, or 42 degrees Celsius, and time of incubation is typically at least 15 seconds, but longer times are preferred to allow binding equilibrium to occur. Particular complexes can be assayed using routine protein binding assays to determine optimal binding conditions for reproducible binding.

The physical parameters of complex formation can be analyzed by quantification of complex formation using assay methods specific for the label used, e.g., liquid scintillation counting for radioactivity detection, enzyme activity for enzyme-labeled moieties, etc. The reaction results are then analyzed utilizing Scatchard analysis, Hill analysis, and other methods commonly known in the arts (see, e.g., *Proteins, Structures, and Molecular Principles*, 2<sup>nd</sup> Edition (1993) Creighton, Ed., W.H. Freeman and Company, New York).

In a second common approach to binding assays, one of the binding species is immobilized on a filter, in a microtiter plate well, in a test tube, to a chromatography matrix, etc., either covalently or non-covalently. Proteins can be covalently immobilized using any method well known in the art, for example, but not limited to the method of Kadonaga and Tjian, 1986, *Proc. Natl. Acad. Sci. USA* 83:5889-5893, i.e., linkage to a cyanogen-bromide derivatized substrate such as CNBr-Sepharose 4B (Pharmacia). Where needed, the use of spacers can reduce steric hindrance by the substrate. Non-covalent attachment of proteins to a substrate include, but are not limited to, attachment of a protein to a charged surface, binding with specific antibodies, binding to a third unrelated interacting protein, etc.

Assays of agents (including cell extracts or a library pool) for competition for binding of one member of a complex (or derivatives thereof) with another member of the complex labeled by any means (e.g., those means described above) are provided to screen for competitors or enhancers of complex formation.

In specific embodiments, blocking agents to inhibit non-specific binding of reagents to other protein components, or absorptive losses of reagents to plastics,

immobilization matrices, etc., are included in the assay mixture. Blocking agents include, but are not restricted to bovine serum albumin,  $\beta$ -casein, nonfat dried milk, Denhardt's reagent, Ficoll, polyvinylpyrrolidone, nonionic detergents (NP40, Triton X-100, Tween 20, Tween 80, etc.), ionic detergents (e.g., SDS, LDS, etc.), polyethylene glycol, etc. Appropriate blocking agent concentrations allow complex formation.

After binding is performed, unbound, labeled protein is removed in the supernatant, and the immobilized protein retaining any bound, labeled protein is washed extensively. The amount of bound label is then quantified using standard methods in the art to detect the label as described, *supra*.

In another specific embodiments screening for modulators of the protein complexes/protein as provided herein can be carried out by attaching those and/or the antibodies as provided herein to a solid carrier. In a further specific embodiment, the invention relates to an array of said molecules.

The preparation of such an array containing different types of proteins, including antibodies) is well known in the art and is apparent to a person skilled in the art (see e.g. Ekins et al., 1989, J. Pharm. Biomed. Anal. 7:155-168; Mitchell et al. 2002, Nature Biotechnol. 20:225-229; Petricoin et al., 2002, Lancet 359:572-577; Templin et al., 2001, Trends Biotechnol. 20:160-166; Wilson and Nock, 2001, Curr. Opin. Chem. Biol. 6:81-85; Lee et al., 2002 Science 295:1702-1705; MacBeath and Schreiber, 2000, Science 289:1760; Blawas and Reichert, 1998, Biomaterials 19:595; Kane et al., 1999, Biomaterials 20:2363; Chen et al., 1997, Science 276:1425; Vaughan et al., 1996, Nature Biotechnol. 14:309-314; Mahler et al., 1997, Immunotechnology 3:31-43; Roberts et al., 1999, Curr. Opin. Chem. Biol. 3:268-273; Nord et al., 1997, Nature Biotechnol. 15:772-777; Nord et al., 2001, Eur. J. Biochem. 268:4269-4277; Brody and Gold, 2000, Rev. Mol. Biotechnol. 74:5-13; Karlstroem and Nygren, 2001, Anal. Biochem. 295:22-30; Nelson et al., 2000, Electrophoresis 21:1155-1163; Honore et al., 2001, Expert Rev. Mol. Diagn. 3:265-274; Albala, 2001, Expert Rev. Mol. Diagn. 2:145-152, Figeys and Pinto, 2001, Electrophoresis 2:208-216 and references in the publications listed here).

Complexes can be attached to an array by different means as will be apparent to a person skilled in the art. Complexes can for example be added to the array via a TAP-tag (as described in WO/0009716 and in Rigaut et al., 1999, Nature Biotechnol. 10:1030-1032) after the purification step or by another suitable purification scheme as will be apparent to a person skilled in the art.

Optionally, the proteins of the complex can be cross-linked to enhance the stability of the complex. Different methods to cross-link proteins are well known in the art. Reactive end-groups of cross-linking agents include but are not limited to -COOH, -SH, -NH<sub>2</sub> or N-oxy-succinamate.

The spacer of the cross-linking agent should be chosen with respect to the size of the complex to be cross-linked. For small protein complexes, comprising only a few proteins, relatively short spacers are preferable in order to reduce the likelihood of cross-linking separate complexes in the reaction mixture. For larger protein complexes, additional use of larger spacers is preferable in order to facilitate cross-linking between proteins within the complex.

It is preferable to check the success-rate of cross-linking before linking the complex to the carrier.

As will be apparent to a person skilled in the art, the optimal rate of cross-linking need to be determined on a case by case basis. This can be achieved by methods well known in the art, some of which are exemplary described below.

A sufficient rate of cross-linking can be checked f.e. by analysing the cross-linked complex vs. a non-cross-linked complex on a denaturing protein gel.

If cross-linking has been performed successfully, the proteins of the complex are expected to be found in the same lane, whereas the proteins of the non-cross-linked complex are expected to be separated according to their individual characteristics. Optionally the presence of all proteins of the complex can be further checked by peptide-sequencing of proteins in the respective bands using methods well known in the art such as mass spectrometry and/or Edman degradation.

In addition, a rate of crosslinking which is too high should also be avoided. If cross-linking has been carried out too extensively, there will be an increasing amount of cross-linking of the individual protein complex, which potentially interferes with a screening for potential binding partners and/or modulators etc. using the arrays.

The presence of such structures can be determined by methods well known in the art and include e.g. gel-filtration experiments comparing the gel filtration profile solutions containing cross-linked complexes vs. uncross-linked complexes.

Optionally, functional assays as will be apparent to a person skilled in the art, some of which are exemplarily provided herein, can be performed to check the integrity of the complex.

Alternatively, members of the protein complex can be expressed as a single fusion protein and coupled to the matrix as will be apparent to a person skilled in the art.

Optionally, the attachment of the complex or proteins or antibody as outlined above can be further monitored by various methods apparent to a person skilled in the art. Those include, but are not limited to surface plasmon resonance (see e.g. McDonnel, 2001, *Curr. Opin. Chem. Biol.* 5:572-577; Lee, 2001, *Trends Biotechnol.* 19:217-222; Weinberger et al., 2000, 1:395-416; Pearson et al., 2000, *Ann. Clin. Biochem.* 37:119-145; Vely et al., 2000, *Methods Mol. Biol.* 121:313-321; Slepak, 2000, *J. Mol. Recognit.* 13:20-26.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Presenilin 1 complex, Sambiasin complex, Presenilin 2 complex, Nicastrin complex, Aph-1a complex, Aph-1b complex, Pen-2 complex, BACE1 D215N complex, APP complex, APP695SW complex, APP-C99 complex, X11beta complex, Fe65 complex, include but are not limited to those described in Vassar R et al., 1999, *Science*, 286:735-41.

Exemplary assays useful for measuring the gamma-secretase activity in vitro of the Presenilin 1 complex and Sambiasin complex include but are not limited to those described in Li Y M et al., 2000, *Proc Natl Acad Sci U S A*, 97:6138-43 and Pinnix I et al., 2001, *J Biol Chem*, 276:481-7.

Exemplary assays useful for measuring the gamma-secretase dependent transcriptional activity of the Presenilin 1 complex and Sambiasin complex include but are not limited to those described in Karlstrom H et al., 2002, *J Biol Chem*, 277:6763-6.

Exemplary assays useful for measuring the formation of amyloid-beta peptides and their aggregated forms of the Presenilin 1 complex include but are not limited to those described in De Strooper B et al., 1998, *Nature*, 391:387-90.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Presenilin 1 complex, Sambiasin complex, Presenilin 2 complex, Nicastrin complex, Aph-1a complex, Aph-1b

complex, Pen-2 complex, BACE1 D215N complex, APP complex, APP695SW complex, APP-C99 complex, X11beta complex, Fe65 complex, include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Presenilin 1 complex, Sambiasin complex, Presenilin 2 complex, Nicastrin complex, Aph-1a complex, Aph-1b complex, Pen-2 complex, BACE1 D215N complex, APP complex, APP695SW complex, APP-C99 complex, X11beta complex, Fe65 complex, include but are not limited to those described in Tian G et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Presenilin 1 complex, Presenilin 2 complex, Nicastrin complex, Aph-1a complex, Aph-1b complex, Pen-2 complex, BACE1 D215N complex, APP complex, APP695SW complex, APP-C99 complex, Fe65 complex, include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring the phosphorylation of Tau proteins in vitro or in cells (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Tau complex include but are not limited to those described in Drewes G et al., 1997, *Cell*, 89:297-308.

Exemplary assays useful for measuring the aggregation of Tau proteins into filaments or tangles in vitro or in cells (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Tau complex include but are not limited to those described in Barghorn S et al., 2000, *Biochemistry*, 39:11714-21.

Exemplary assays useful for measuring the transactivation of reporter genes by APP-Gal4/VP16 (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the X11beta complex include but are not limited to those described in Biederer T et al., 2002, *J Neurosci*, 22:7340-51.

Exemplary assays useful for measuring the activation of Calsenilin target genes including prodynorphin that contain DRE elements (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Calsenilin complex include but are not limited to those described in Cheng Hai-Ying M et al., 2002, Cell, 108:31-43.

Exemplary assays useful for measuring the activation or inactivation of potassium channels by compounds (e.g. Retigabine) and their effect on transcriptional processes regulated directly or indirectly by Calsenilin of the Calsenilin complex include but are not limited to those described in Rundfeldt C et al., 1997, Eur J Pharmacol, 336:243-9.

#### 4.6.1 CANDIDATE MOLECULES

Any molecule known in the art can be tested for its ability to modulate (increase or decrease) the amount of, activity of, or protein component composition of a complex of the present invention as detected by a change in the amount of, activity of, or protein component composition of, said complex. By way of example, a change in the amount of the complex can be detected by detecting a change in the amount of the complex that can be isolated from a cell expressing the complex machinery. For identifying a molecule that modulates complex activity, candidate molecules can be directly provided to a cell expressing the complex machinery, or, in the case of candidate proteins, can be provided by providing their encoding nucleic acids under conditions in which the nucleic acids are recombinantly expressed to produce the candidate proteins within the cell expressing the complex machinery, the complex is then isolated from the cell and the isolated complex is assayed for activity using methods well known in the art, not limited to those described, supra.

This embodiment of the invention is well suited to screen chemical libraries for molecules which modulate, e.g., inhibit, antagonize, or agonize, the amount of, activity of, or protein component composition of the complex. The chemical libraries can be peptide libraries, peptidomimetic libraries, chemically synthesized libraries, recombinant, e.g., phage display libraries, and in vitro translation-based libraries, other non-peptide synthetic organic libraries, etc.

Exemplary libraries are commercially available from several sources (ArQule, Tripos/PanLabs, ChemDesign, Pharmacopoeia). In some cases, these chemical

libraries are generated using combinatorial strategies that encode the identity of each member of the library on a substrate to which the member compound is attached, thus allowing direct and immediate identification of a molecule that is an effective modulator. Thus, in many combinatorial approaches, the position on a plate of a compound specifies that compound's composition. Also, in one example, a single plate position may have from 1-20 chemicals that can be screened by administration to a well containing the interactions of interest. Thus, if modulation is detected, smaller and smaller pools of interacting pairs can be assayed for the modulation activity. By such methods, many candidate molecules can be screened.

Many diversity libraries suitable for use are known in the art and can be used to provide compounds to be tested according to the present invention. Alternatively, libraries can be constructed using standard methods. Chemical (synthetic) libraries, recombinant expression libraries, or polysome-based libraries are exemplary types of libraries that can be used.

The libraries can be constrained or semirigid (having some degree of structural rigidity), or linear or unconstrained. The library can be a cDNA or genomic expression library, random peptide expression library or a chemically synthesized random peptide library, or non-peptide library. Expression libraries are introduced into the cells in which the assay occurs, where the nucleic acids of the library are expressed to produce their encoded proteins.

In one embodiment, peptide libraries that can be used in the present invention may be libraries that are chemically synthesized in vitro. Examples of such libraries are given in Houghten et al., 1991, *Nature* 354:84-86, which describes mixtures of free hexapeptides in which the first and second residues in each peptide were individually and specifically defined; Lam et al., 1991, *Nature* 354:82-84, which describes a "one bead, one peptide" approach in which a solid phase split synthesis scheme produced a library of peptides in which each bead in the collection had immobilized thereon a single, random sequence of amino acid residues; Medynski, 1994, *Bio/Technology* 12:709-710, which describes split synthesis and T-bag synthesis methods; and Gallop et al., 1994, *J. Med. Chem.* 37:1233-1251. Simply by way of other examples, a combinatorial library may be prepared for use, according to the methods of Ohlmeyer et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:10922-10926; Erb et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:11422-11426; Houghten et al., 1992, *Biotechniques* 13:412; Jayawickreme et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:1614-1618; or Salmon et al., 1993, *Proc. Natl. Acad.*

Sci. USA 90:11708-11712. PCT Publication No. WO 93/20242 and Brenner and Lerner, 1992, Proc. Natl. Acad. Sci. USA 89:5381-5383 describe "encoded combinatorial chemical libraries," that contain oligonucleotide identifiers for each chemical polymer library member.

In a preferred embodiment, the library screened is a biological expression library that is a random peptide phage display library, where the random peptides are constrained (e.g., by virtue of having disulfide bonding).

Further, more general, structurally constrained, organic diversity (e.g., nonpeptide) libraries, can also be used. By way of example, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) may be used.

Conformationally constrained libraries that can be used include but are not limited to those containing invariant cysteine residues which, in an oxidizing environment, cross-link by disulfide bonds to form cystines, modified peptides (e.g., incorporating fluorine, metals, isotopic labels, are phosphorylated, etc.), peptides containing one or more non-naturally occurring amino acids, non-peptide structures, and peptides containing a significant fraction of  $\gamma$ -carboxyglutamic acid.

Libraries of non-peptides, e.g., peptide derivatives (for example, that contain one or more non-naturally occurring amino acids) can also be used. One example of these are peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371). Peptoids are polymers of non-natural amino acids that have naturally occurring side chains attached not to the  $\alpha$  carbon but to the backbone amino nitrogen. Since peptoids are not easily degraded by human digestive enzymes, they are advantageously more easily adaptable to drug use. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al., 1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

The members of the peptide libraries that can be screened according to the invention are not limited to containing the 20 naturally occurring amino acids. In particular, chemically synthesized libraries and polysome based libraries allow the use of amino acids in addition to the 20 naturally occurring amino acids (by their inclusion in the precursor pool of amino acids used in library production). In specific embodiments, the library members contain one or more non-natural or non-classical amino acids or cyclic peptides. Non-classical amino acids include but are not limited to the D-isomers of the common amino acids,  $\gamma$ -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric

acid;  $\gamma$ -Abu,  $\gamma$ -Ahx, 6-amino hexanoic acid; Aib, 2-amino isobutyric acid; 3-amino propionic acid; ornithine; norleucine; norvaline, hydroxyproline, sarcosine, citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine,  $\beta$ -alanine, designer amino acids such as  $\beta$ -methyl amino acids,  $\gamma$ -methyl amino acids, N-methyl amino acids, fluoro-amino acids and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

In a specific embodiment, fragments and/or analogs of complexes of the invention, or protein components thereof, especially peptidomimetics, are screened for activity as competitive or non-competitive inhibitors of complex activity or formation.

In another embodiment of the present invention, combinatorial chemistry can be used to identify modulators of a the complexes. Combinatorial chemistry is capable of creating libraries containing hundreds of thousands of compounds, many of which may be structurally similar. While high throughput screening programs are capable of screening these vast libraries for affinity for known targets, new approaches have been developed that achieve libraries of smaller dimension but which provide maximum chemical diversity. (See e.g., Matter, 1997, J. Med. Chem. 40:1219-1229).

One method of combinatorial chemistry, affinity fingerprinting, has previously been used to test a discrete library of small molecules for binding affinities for a defined panel of proteins. The fingerprints obtained by the screen are used to predict the affinity of the individual library members for other proteins or receptors of interest (in the instant invention, the protein complexes of the present invention and protein components thereof.) The fingerprints are compared with fingerprints obtained from other compounds known to react with the protein of interest to predict whether the library compound might similarly react. For example, rather than testing every ligand in a large library for interaction with a complex or protein component, only those ligands having a fingerprint similar to other compounds known to have that activity could be tested. (See, e.g., Kauvar et al., 1995, Chem. Biol. 2:107-118; Kauvar, 1995, Affinity fingerprinting, Pharmaceutical Manufacturing International. 8:25-28; and Kauvar, Toxic-Chemical Detection by Pattern Recognition in New Frontiers in Agrochemical Immunoassay, Kurtz, Stanker and Skerritt (eds), 1995, AOAC: Washington, D.C., 305-312).

Kay et al. (1993, Gene 128:59-65) disclosed a method of constructing peptide libraries that encode peptides of totally random sequence that are longer than those of any prior conventional libraries. The libraries disclosed in Kay et al. encode totally synthetic random peptides of greater than about 20 amino acids in length. Such libraries

can be advantageously screened to identify complex modulators. (See also U.S. Patent No. 5,498,538 dated March 12, 1996; and PCT Publication No. WO 94/18318 dated August 18, 1994).

A comprehensive review of various types of peptide libraries can be found in Gallop et al., 1994, J. Med. Chem. 37:1233-1251.

#### 4.7 PHARMACEUTICAL COMPOSITIONS AND THERAPEUTIC/PROPHYLACTIC ADMINISTRATION

The invention provides methods of treatment (and prophylaxis) by administration to a subject of an effective amount of a therapeutic of the invention. In a preferred aspect, the therapeutic is substantially purified. The subject is preferably an animal including, but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human. In a specific embodiment, a non-human mammal is the subject.

Various delivery systems are known and can be used to administer a therapeutic of the invention, e.g., encapsulation in liposomes, microparticles, and microcapsules; use of recombinant cells capable of expressing the therapeutic, use of receptor-mediated endocytosis (e.g., Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432); construction of a therapeutic nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds may be administered by any convenient route, for example by infusion, by bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral, rectal and intestinal mucosa, etc.), and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment. This may be

achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. In one embodiment, administration can be by direct injection at the site (or former site) of a malignant tumor or neoplastic or pre-neoplastic tissue.

In another embodiment, the therapeutic can be delivered in a vesicle, in particular a liposome (Langer, 1990, *Science* 249:1527-1533; Treat et al., 1989, In: *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler, eds., Liss, New York, pp. 353-365; Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)

In yet another embodiment, the therapeutic can be delivered via a controlled release system. In one embodiment, a pump may be used (Langer, *supra*; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:201-240; Buchwald et al., 1980, *Surgery* 88:507-516; Saudek et al., 1989, *N. Engl. J. Med.* 321:574-579). In another embodiment, polymeric materials can be used (*Medical Applications of Controlled Release*, Langer and Wise, eds., CRC Press, Boca Raton, Florida, 1974; *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball, eds., Wiley, New York, 1984; Ranger and Peppas, 1983, *Macromol. Sci. Rev. Macromol. Chem.* 23:61; Levy et al., 1985, *Science* 228:190-192; During et al., 1989, *Ann. Neurol.* 25:351-356; Howard et al., 1989, *J. Neurosurg.* 71:858-863). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (e.g., Goodson, 1984, In: *Medical Applications of Controlled Release*, *supra*, Vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer (1990, *Science* 249:1527-1533).

In a specific embodiment where the therapeutic is a nucleic acid encoding a protein therapeutic, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or by coating it with lipids, cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (e.g., Joliot et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:1864-1868), etc. Alternatively, a nucleic acid therapeutic can be introduced

intracellularly and incorporated by homologous recombination within host cell DNA for expression.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a therapeutic, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are preferred carriers when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are preferably employed as liquid carriers for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the therapeutic, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated, in accordance with routine procedures, as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration

are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lidocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water-free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water or saline for injection can be provided so that the ingredients may be mixed prior to administration.

The therapeutics of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free carboxyl groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., those formed with free amine groups such as those derived from isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc., and those derived from sodium, potassium, ammonium, calcium, and ferric hydroxides, etc.

The amount of the therapeutic of the invention which will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. However, suitable dosage ranges for intravenous administration are generally about 20-500 micrograms of active compound per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 pg/kg body weight to 1 mg/kg body weight. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

Suppositories generally contain active ingredient in the range of 0.5% to 10% by weight; oral formulations preferably contain 10% to 95% active ingredient.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of

pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. For example, the kit can comprise in one or more containers a first protein, or a functionally active fragment or functionally active derivative thereof, which first protein is selected from the group consisting of proteins listed in the third column of table 1; and a second protein, or a functionally active fragment or functionally active derivative thereof, which second protein is selected from the group consisting of proteins listed in the fourth column of table 1.

Alternatively, the kit can comprise in one or more containers, all proteins, functionally active fragments or functionally active derivatives thereof of from the group of proteins in the fifth column of table 1.

The kits of the present invention can also contain expression vectors encoding the essential components of the complex machinery, which components after being expressed can be reconstituted in order to form a biologically active complex. Such a kit preferably also contains the required buffers and reagents. Optionally associated with such container(s) can be instructions for use of the kit and/or a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

#### 4.8 ANIMAL MODELS

The present invention also provides animal models. In one embodiment, animal models for diseases and disorders involving the protein complexes of the present invention are provided. These animal models are well known in the art. These animal models include, but are not limited to those which are listed in the section 4.6 (supra) as exemplary animal models to study any of the complexes provided in the invention. Such animals can be initially produced by promoting homologous recombination or insertional mutagenesis between genes encoding the protein components of the complexes in the chromosome, and exogenous genes encoding the protein components of the complexes that have been rendered biologically inactive or deleted (preferably by insertion of a

heterologous sequence, e.g., an antibiotic resistance gene). In a preferred aspect, homologous recombination is carried out by transforming embryo-derived stem (ES) cells with one or more vectors containing one or more insertionally inactivated genes, such that homologous recombination occurs, followed by injecting the transformed ES cells into a blastocyst, and implanting the blastocyst into a foster mother, followed by the birth of the chimeric animal ("knockout animal") in which a gene encoding a component protein from the third column of table 1, or a functionally active fragment or functionally active derivative thereof, and a gene encoding a component protein from the fourth column of table 1, or a functionally active fragment or functionally active derivative thereof, has been inactivated or deleted (Capecchi, 1989, Science 244:1288-1292).

In another preferred aspect, homologous recombination is carried out by transforming embryo-derived stem (ES) cells with one or more vectors containing one or more insertionally inactivated genes, such that homologous recombination occurs, followed by injecting the transformed ES cells into a blastocyst, and implanting the blastocyst into a foster mother, followed by the birth of the chimeric animal ("knockout animal") in which the genes of all component proteins from the group of proteins listed in the third column of table 1 or of all proteins from the group of proteins listed in the forth column of table 1 have been inactivated or deleted.

The chimeric animal can be bred to produce additional knockout animals. Such animals can be mice, hamsters, sheep, pigs, cattle, etc., and are preferably non-human mammals. In a specific embodiment, a knockout mouse is produced.

Such knockout animals are expected to develop, or be predisposed to developing, diseases or disorders associated with mutations involving the protein complexes of the present invention, and thus, can have use as animal models of such diseases and disorders, e.g., to screen for or test molecules (e.g., potential therapeutics) for such diseases and disorders.

In a different embodiment of the invention, transgenic animals that have incorporated and express (or over-express or mis-express) a functional gene encoding a protein component of the complex, e.g. by introducing the a gene encoding one or more of the components of the complex under the control of a heterologous promoter (i.e., a promoter that is not the native promoter of the gene) that either over-expresses the protein or proteins, or expresses them in tissues not normally expressing the complexes or proteins, can have use as animal models of diseases and disorders characterized by

elevated levels of the protein complexes. Such animals can be used to screen or test molecules for the ability to treat or prevent the diseases and disorders cited supra.

In one embodiment, the present invention provides a recombinant non-human animal in which an endogenous gene encoding a first protein, or a functionally active fragment or functionally active derivative thereof, which first protein is selected from the group of proteins listed in the third column of table 1, and an endogenous gene encoding a second protein, or a functionally active fragment or functionally active derivative thereof, which second protein is selected from the group consisting of proteins listed in the fourth column of table 1 has been deleted or inactivated by homologous recombination or insertional mutagenesis of said animal or an ancestor thereof. In addition, the present invention provides a recombinant non-human animal in which the endogenous genes of all proteins, or functionally active fragments or functionally active derivatives thereof of one of the group of proteins listed in the fifth column have been deleted or inactivated by homologous recombination or insertional mutagenesis of said animal or an ancestor thereof:

In another embodiment, the present invention provides a recombinant non-human animal in which an endogenous gene encoding a first protein, or a functionally active fragment or functionally active derivative thereof, which first protein is selected from the group consisting of proteins of the third column of table 1, and an endogenous gene encoding a second protein, or a functionally active fragment or functionally active derivative thereof, which second protein is selected from the group consisting of proteins of the fourth column, of table 1 are recombinantly expressed in said animal or an ancestor thereof.

The following series of examples are presented by way of illustration and not by way of limitation on the scope of the invention.

## EXAMPLES

An object of the present invention was to identify protein complexes of the APP processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the complexes of the APP

processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

By applying the process according to the invention said complexes were identified. The components are listed in table 1.

Those complexes are, as called herein, the following complexes: Presenilin 1 complex, Sambiasin complex, Presenilin 2 complex, Nicastrin complex, Aph-1a complex, Aph-1b complex, Pen-2 complex, BACE1 N215D complex, APP complex, APP695SW complex, APP-C99 complex, Tau complex, X11beta complex, Fe65 complex and Calsenilin complex.

Said object is further achieved by the characterization of component proteins. These proteins are listed in table 2.

Thus, the invention relates to the following embodiments:

Thus the invention relates to the Presenilin 1 complex:

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "Alpha catenin" (SEQ ID No:1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha catenin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha catenin" nucleic acid or its complement under low stringency conditions,
    - (ii) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,
    - (iii) "Beta catenin" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Beta catenin", the variant being encoded by a nucleic acid that hybridizes to the "Beta catenin" nucleic acid or its complement under low stringency conditions,
    - (iv) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions,

- (v) "Delta-2 catenin" (SEQ ID No:9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-2 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-2 catenin" nucleic acid or its complement under low stringency conditions,
- (vi) "Gamma catenin" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Gamma catenin", the variant being encoded by a nucleic acid that hybridizes to the "Gamma catenin" nucleic acid or its complement under low stringency conditions,
- (vii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (viii) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,
- (ix) "Plakophilin 4" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Plakophilin 4", the variant being encoded by a nucleic acid that hybridizes to the "Plakophilin 4" nucleic acid or its complement under low stringency conditions,
- (x) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and
- (xi) "Ubiquilin" (SEQ ID No:20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquilin", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquilin" nucleic acid or its complement under low stringency conditions, and
- (b) at least one second protein, which second protein is selected from the group consisting of:
  - (i) "BAX inhibitor 1" (SEQ ID No:3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BAX inhibitor 1", the variant being encoded by a nucleic acid that hybridizes to the "BAX inhibitor 1" nucleic acid or its complement under low stringency conditions,

- (ii) "CGI-147" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-147", the variant being encoded by a nucleic acid that hybridizes to the "CGI-147" nucleic acid or its complement under low stringency conditions,
- (iii) "Cadherin-11 precursor" (SEQ ID No:6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin-11 precursor", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin-11 precursor" nucleic acid or its complement under low stringency conditions,
- (iv) "Cadherin-4 precursor" (SEQ ID No:7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin-4 precursor", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin-4 precursor" nucleic acid or its complement under low stringency conditions,
- (v) "FKRP" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FKRP", the variant being encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (vi) "FLJ20627" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20627", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20627" nucleic acid or its complement under low stringency conditions,
- (vii) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,
- (viii) "Sortilin 1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin 1" nucleic acid or its complement under low stringency conditions, and
- (ix) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency

conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. The protein complex according to No. 1 wherein the first protein is the protein "Presenilin 1" (SEQ ID No:17), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid under low stringency conditions.

3. The protein complex according to No. 1 comprising the following proteins:

- (i) "Alpha catenin" (SEQ ID No:1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha catenin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha catenin" nucleic acid or its complement under low stringency conditions,
- (ii) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,
- (iii) "BAX inhibitor 1" (SEQ ID No:3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BAX inhibitor 1", the variant being encoded by a nucleic acid that hybridizes to the "BAX inhibitor 1" nucleic acid or its complement under low stringency conditions,
- (iv) "Beta catenin" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Beta catenin", the variant being encoded by a nucleic acid that hybridizes to the "Beta catenin" nucleic acid or its complement under low stringency conditions,
- (v) "CGI-147" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-147", the variant being encoded by a nucleic acid that hybridizes to the "CGI-147" nucleic acid or its complement under low stringency conditions,

- (vi) "Cadherin-11 precursor" (SEQ ID No:6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin-11 precursor", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin-11 precursor" nucleic acid or its complement under low stringency conditions,
- (vii) "Cadherin-4 precursor" (SEQ ID No:7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin-4 precursor", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin-4 precursor" nucleic acid or its complement under low stringency conditions,
- (viii) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions,
- (ix) "Delta-2 catenin" (SEQ ID No:9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-2 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-2 catenin" nucleic acid or its complement under low stringency conditions,
- (x) "FKRP" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FKRP", the variant being encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (xi) "FLJ20627" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20627", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20627" nucleic acid or its complement under low stringency conditions,
- (xii) "Gamma catenin" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Gamma catenin", the variant being encoded by a nucleic acid that hybridizes to the "Gamma catenin" nucleic acid or its complement under low stringency conditions,
- (xiii) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,
- (xiv) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin",

the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(xv) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,

(xvi) "Plakophilin 4" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Plakophilin 4", the variant being encoded by a nucleic acid that hybridizes to the "Plakophilin 4" nucleic acid or its complement under low stringency conditions,

(xvii) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,

(xviii) "Sortilin 1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin 1" nucleic acid or its complement under low stringency conditions,

(xix) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions, and/or

(xx) "Ubiquilin" (SEQ ID No:20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquilin", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquilin" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising at least 12 but no more than 19 of the following proteins:

(i) "Alpha catenin" (SEQ ID No:1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha catenin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha catenin" nucleic acid or its complement under low stringency conditions,

- (ii) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,
- (iii) "BAX inhibitor 1" (SEQ ID No:3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BAX inhibitor 1", the variant being encoded by a nucleic acid that hybridizes to the "BAX inhibitor 1" nucleic acid or its complement under low stringency conditions,
- (iv) "Beta catenin" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Beta catenin", the variant being encoded by a nucleic acid that hybridizes to the "Beta catenin" nucleic acid or its complement under low stringency conditions,
- (v) "CGI-147" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-147", the variant being encoded by a nucleic acid that hybridizes to the "CGI-147" nucleic acid or its complement under low stringency conditions,
- (vi) "Cadherin-11 precursor" (SEQ ID No:6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin-11 precursor", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin-11 precursor" nucleic acid or its complement under low stringency conditions,
- (vii) "Cadherin-4 precursor" (SEQ ID No:7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin-4 precursor", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin-4 precursor" nucleic acid or its complement under low stringency conditions,
- (viii) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions,
- (ix) "Delta-2 catenin" (SEQ ID No:9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-2 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-2 catenin" nucleic acid or its complement under low stringency conditions,
- (x) "FKRP" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FKRP", the variant being

encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,

(xi) "FLJ20627" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20627", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20627" nucleic acid or its complement under low stringency conditions,

(xii) "Gamma catenin" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Gamma catenin", the variant being encoded by a nucleic acid that hybridizes to the "Gamma catenin" nucleic acid or its complement under low stringency conditions,

(xiii) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,

(xiv) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(xv) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,

(xvi) "Plakophilin 4" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Plakophilin 4", the variant being encoded by a nucleic acid that hybridizes to the "Plakophilin 4" nucleic acid or its complement under low stringency conditions,

(xvii) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,

(xviii) "Sortilin 1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin 1" nucleic acid or its complement under low stringency conditions,

(xix) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions,

(xx) "Ubiquilin" (SEQ ID No:20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquilin", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquilin" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the gamma-secretase activity.

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:

expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Presenilin 1 complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the Presenilin 1 complex selected from:

- (i) "CGI-147" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-147", the variant being encoded by a nucleic acid that hybridizes to the "CGI-147" nucleic acid or its complement under low stringency conditions,
- (ii) "FKRP" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FKRP", the variant being encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (iii) "FLJ20627" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20627", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20627" nucleic acid or its complement under low stringency conditions,
- (iv) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions, and
- (v) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA,

and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising:

(a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or

(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b) or

(c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container:

(a) the complex of any of No. 1 - 8 and/or the proteins of No. 13 and/or

- (b) an antibody according to No. 17 and/or
- (c) a nucleic acid encoding a protein of the complex of any of No. 1 – 8 and/or a protein of No. 13 and/or
- (d) cells expressing the complex of any of No. 1 – 8 and/or a protein of No. 13 and, optionally,
- (e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as a neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for modifying a physiological substrate of the complex comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "CGI-147" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-147", the variant being encoded by a nucleic acid that hybridizes to the "CGI-147" nucleic acid or its complement under low stringency conditions,
- (ii) "FKRP" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FKRP", the variant being encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (iii) "FLJ20627" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20627",

the variant being encoded by a nucleic acid that hybridizes to the "FLJ20627" nucleic acid or its complement under low stringency conditions,

(iv) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions, and/or

(v) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to a complex of any one of No. 1 - 8 and/or any of the following the proteins:

(i) "CGI-147" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-147", the variant being encoded by a nucleic acid that hybridizes to the "CGI-147" nucleic acid or its complement under low stringency conditions,

(ii) "FKRP" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FKRP", the variant being encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,

(iii) "FLJ20627" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20627", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20627" nucleic acid or its complement under low stringency conditions,

(iv) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442",

the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions, and/or

(v) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions, comprising the steps of:

- (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and
- (b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:

- (a) exposing said complex, or a cell or organism containing Presenilin 1 complex to one or more candidate molecules; and
- (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether

- (i) "Alpha catenin" (SEQ ID No:1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha catenin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha catenin" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "BAX inhibitor 1" (SEQ ID No:3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BAX inhibitor 1", the variant being encoded by a nucleic acid that hybridizes to the "BAX inhibitor 1" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Beta catenin" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Beta catenin", the variant being encoded by a nucleic acid that hybridizes to the "Beta catenin" nucleic acid or its complement under low stringency conditions, and/or
- (v) "CGI-147" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-147", the variant being encoded by a nucleic acid that hybridizes to the "CGI-147" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "Cadherin-11 precursor" (SEQ ID No:6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin-11 precursor", the variant being encoded by a nucleic acid that hybridizes to the

"Cadherin-11 precursor" nucleic acid or its complement under low stringency conditions, and/or

(vii) "Cadherin-4 precursor" (SEQ ID No:7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin-4 precursor", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin-4 precursor" nucleic acid or its complement under low stringency conditions, and/or

(viii) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions, and/or

(ix) "Delta-2 catenin" (SEQ ID No:9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-2 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-2 catenin" nucleic acid or its complement under low stringency conditions, and/or

(x) "FKRP" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FKRP", the variant being encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and/or

(xi) "FLJ20627" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20627", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20627" nucleic acid or its complement under low stringency conditions, and/or

(xii) "Gamma catenin" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Gamma catenin", the variant being encoded by a nucleic acid that hybridizes to the "Gamma catenin" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

- (xv) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "Plakophilin 4" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Plakophilin 4", the variant being encoded by a nucleic acid that hybridizes to the "Plakophilin 4" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "Sortilin 1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin 1" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "Ubiquilin" (SEQ ID No:20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquilin", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquilin" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether

- (i) "Alpha catenin" (SEQ ID No:1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha catenin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha catenin" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "BAX inhibitor 1" (SEQ ID No:3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BAX inhibitor 1", the variant being encoded by a nucleic acid that hybridizes to the "BAX inhibitor 1" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Beta catenin" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Beta catenin", the variant being encoded by a nucleic acid that hybridizes to the "Beta catenin" nucleic acid or its complement under low stringency conditions, and/or
- (v) "CGI-147" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-147", the variant being encoded by a nucleic acid that hybridizes to the "CGI-147" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "Cadherin-11 precursor" (SEQ ID No:6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin-11 precursor", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin-11 precursor" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "Cadherin-4 precursor" (SEQ ID No:7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin-4 precursor", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin-4 precursor" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions, and/or

- (ix) "Delta-2 catenin" (SEQ ID No:9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-2 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-2 catenin" nucleic acid or its complement under low stringency conditions, and/or
- (x) "FKRP" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FKRP", the variant being encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "FLJ20627" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20627", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20627" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "Gamma catenin" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Gamma catenin", the variant being encoded by a nucleic acid that hybridizes to the "Gamma catenin" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "Plakophilin 4" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Plakophilin 4", the variant being encoded by a nucleic acid that hybridizes to the "Plakophilin 4" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin

1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and/or  
 (xviii) "Sortilin 1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin 1" nucleic acid or its complement under low stringency conditions, and/or  
 (xix) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions, and/or  
 (xx) "Ubiquilin" (SEQ ID No:20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquilin", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquilin" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the gamma-secretase activity of, or the protein composition of said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins:

- (i) "Alpha catenin" (SEQ ID No:1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha catenin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha catenin" nucleic acid or its complement under low stringency conditions,
- (ii) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,
- (iii) "BAX inhibitor 1" (SEQ ID No:3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BAX inhibitor 1", the variant being encoded by a nucleic acid that hybridizes to the "BAX inhibitor 1" nucleic acid or its complement under low stringency conditions,
- (iv) "Beta catenin" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Beta catenin", the variant being encoded by a nucleic acid that hybridizes to the "Beta catenin" nucleic acid or its complement under low stringency conditions,
- (v) "CGI-147" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-147", the variant being encoded by a nucleic acid that hybridizes to the "CGI-147" nucleic acid or its complement under low stringency conditions,
- (vi) "Cadherin-11 precursor" (SEQ ID No:6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin-11 precursor", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin-11 precursor" nucleic acid or its complement under low stringency conditions,
- (vii) "Cadherin-4 precursor" (SEQ ID No:7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin-4 precursor", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin-4 precursor" nucleic acid or its complement under low stringency conditions,
- (viii) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions,

- (ix) "Delta-2 catenin" (SEQ ID No:9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-2 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-2 catenin" nucleic acid or its complement under low stringency conditions,
- (x) "FKRP" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FKRP", the variant being encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (xi) "FLJ20627" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20627", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20627" nucleic acid or its complement under low stringency conditions,
- (xii) "Gamma catenin" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Gamma catenin", the variant being encoded by a nucleic acid that hybridizes to the "Gamma catenin" nucleic acid or its complement under low stringency conditions,
- (xiii) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,
- (xiv) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (xv) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,
- (xvi) "Plakophilin 4" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Plakophilin 4", the variant being encoded by a nucleic acid that hybridizes to the "Plakophilin 4" nucleic acid or its complement under low stringency conditions,
- (xvii) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin

1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,

(xviii) "Sortilin 1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin 1" nucleic acid or its complement under low stringency conditions,

(xix) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions, and/or(xx) "Ubiquilin" (SEQ ID No:20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquilin", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquilin" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

The invention further relates to the Sambiasin complex:

1. A protein complex comprising

(a) a first protein, or a functionally active fragment or functionally active derivative thereof, which first protein is selected from the group consisting of:

(i) Sambiasin-1 (SEQ ID No:267) or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein or its complement under low stringency conditions,

(b) a second protein, or a functionally active fragment or functionally active derivative thereof, which second protein is selected from the group consisting of:

(i) Presenilin-1 (SEQ ID No:17), or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein or its complement under low stringency conditions,

(ii) Nicastrin (SEQ ID No:14), or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein or its complement under low stringency conditions, wherein said first protein and said second protein are members of a native cellular complex, and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. A protein complex comprising Sambiasin-1 (SEQ ID No:267) or Sambiasin-2 (SEQ ID No:208) and Presenilin1 (SEQ ID No:17) or Presenilin-2 (SEQ ID No:152).
3. A protein complex according to No. 1 or 2 further comprising Nicastrin (SEQ ID No:14)
4. A protein complex according to any of No. 1 - 3 comprising Sambiasin-1 (SEQ ID No:267) and Presenilin-1 (SEQ ID No:17) and Nicastrin (SEQ ID No:14).
5. The complex of any No. 1 - 4 comprising a functionally active derivative of any of the proteins of said complex, wherein the functionally active derivative is a fusion protein comprising said protein fused to an amino acid sequence different from said protein.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said protein fused to an affinity tag or label.
7. The complex of any No. 1 - 4 comprising a fragment of any of the proteins of said complex, which fragment binds to another protein component of said complex.
8. The complex of any No. 1 - 7 that is involved in the gamma-secretase activity.
9. Protein comprising the amino acid sequence of SEQ ID No:267, or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein or its complement under low

stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C, with the proviso that the protein does not have the amino acid sequence according to SEQ ID No:268.

10. Protein comprising the amino acid sequence of SEQ ID No:267.

11. Nucleic acid encoding a protein according to No. 9 or 10.

12. Construct, preferably a vector construct, comprising

(a) a nucleic acid according to No. 11 and at least one further nucleic acid which is normally not associated with said nucleic acid, or

(b) at least two separate nucleic acid sequences each encoding a different protein of any of the proteins, or a functionally active fragment or a functionally active derivative thereof according to No. 1 or,

(c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

13. Host cell, containing a vector comprising at least one of the nucleic acid of No. 11 and/or any of the constructs of No. 12 or containing several vectors each comprising at least one nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1.

14. An antibody or a fragment of said antibody containing the binding domain thereof, which binds the complex of any No. 1 - 8 and which does not bind the first protein when uncomplexed or the second protein when uncomplexed and/or an antibody or a fragment

of said antibody containing the binding domain thereof which binds to any of the group of proteins according to any of No. 9 or 10.

15. A kit comprising in one or more container:

- (a) the complex of any of No. 1 – 8 and/or the proteins of No. 9 or 10 and/or
- (b) an antibody according to No. 14 and/or
- (c) a nucleic acid encoding a protein of the complex of any of No. 1 – 8 and/or a protein of No. 9 or 10 and/or
- (d) cells expressing the complex of any of No. 1 – 8 and/or a protein of No. 9 or 10 and optionally
- (e) further components such as reagents, buffers and working instructions.

16. A kit according to No. 15 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and developmental disorders caused by defects in the Notch pathway.

17. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or any of the proteins of any of No. 9 or 10 and/or at least one antibody according to No. 14 is attached to a solid carrier.

18. A process for modifying the physiological substrates of any of the complexes of any of No. 1 - 4 comprising the step of bringing into contact a complex of any of No. 1 - 7 with said substrate, such that said substrate is modified.

19. A pharmaceutical composition comprising the protein complex of any No. 1 - 8 and a pharmaceutically acceptable carrier and/or any of the proteins of No. 9 or 10 and a pharmaceutically acceptable carrier.

20. A pharmaceutical composition according to No. 19 for the treatment of diseases and disorders such as neurodegenerative diseases, such as Alzheimer's disease, and/or developmental disorders caused by defects in the Notch pathway.

21. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the proteins of No. 9 or 10, comprising the following steps:

- (a) exposing said complex or protein, or a cell or organism containing same, to one or more candidate molecules; and
- (b) determining whether said candidate molecule is bound to the complex or protein.

22. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:

- (a) exposing said complex, or a cell or organism containing said complex to one or more candidate molecules; and
- (b) determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

23. The method of No. 22 wherein the amount of said complex is determined.

24. The method of No. 22, wherein the activity of said complex is determined.

25. The method of No. 24, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a physiological substrate of any of the complexes according to any of No. 1 - 4 and determine whether said substrate is processed.

26. The method of No. 22, wherein the amounts of the individual protein components of said complex are determined.

27. The method of No. 26, wherein said determining step comprises determining whether

- (i) Sambiasin-1 (SEQ ID No:267) or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein or its complement under low stringency conditions, and/or
- (ii) Presenilin-1 (SEQ ID No:17), or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein or its complement under low stringency conditions, and/or
- (iii) Nicastrin (SEQ ID No:14), or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein or its complement under low stringency conditions,

are present in the complex and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

28. The method of any of No. 22 - 27, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and developmental disorders caused by defects in the Notch pathway.

29. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and developmental disorders caused by defects in the Notch pathway.

30. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 22 - 27 to identify a molecule that modulates the function,

activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

31. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, component composition of, or intracellular localization of the complex of any one of No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

32. The method of No. 31, wherein the amount of said complex is determined.

33. The method of No. 31, wherein the activity of said complex is determined.

34. The method of No. 33, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a physiological substrate of any of the complexes according to any of No. 1 - 4 and determine whether said substrate is processed.

35. The method of No. 31, wherein the amount of the individual protein components of said complex are determined.

36. The method of No. 35, wherein said determining step comprises determining whether (i) Sambiasin-1 (SEQ ID No:267) or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein or its complement under low stringency conditions, and/or

(ii) Presenilin-1 (SEQ ID No:17), or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein or its complement under low stringency conditions, and/or

(iii) Nicastrin (SEQ ID No:14), or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein or its complement under low stringency conditions,

are present in the complex and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

37. The complex of any one of No. 1 - 8, or proteins of any of No. 9 or 10 or the antibody or fragment of No. 14, for use in a method of diagnosing a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and developmental disorders caused by defects in the Notch pathway.

38. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity of, component composition of or intracellular localization of, the complex of anyone of No. 1 - 8 comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the gamma-secretase activity of, or protein components of, said complex.

39. The method according to No. 38, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

40. The method according to No. 39, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

41. Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) Sambiasin-1 (SEQ ID No:267) or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein or its complement under low stringency conditions, or

(ii) Presenilin-1 (SEQ ID No:17), or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein or its complement under low stringency conditions, or

(iii) Nicastrin (SEQ ID No:14), or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and developmental disorders caused by defects in the Notch pathway.

The invention further relates to the Fe65 complex:

1. A protein complex selected from complex (I) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "APLP1" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP1", the variant being encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(ii) "APLP2" (SEQ ID No:28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP2", the variant being encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

- (iii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "APP-C99" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP-C99", the variant being encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (v) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (vi) "RNB6" (SEQ ID No:40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RNB6", the variant being encoded by a nucleic acid that hybridizes to the "RNB6" nucleic acid or its complement under low stringency conditions, and
- (vii) "Transcription factor CP2 " (SEQ ID No:42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Transcription factor CP2 ", the variant being encoded by a nucleic acid that hybridizes to the "Transcription factor CP2 " nucleic acid or its complement under low stringency conditions, and
- (b) at least one second protein, which second protein is selected from the group consisting of:
  - (i) "14-3-3 protein epsilon" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein epsilon", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein epsilon" nucleic acid or its complement under low stringency conditions,
  - (ii) "14-3-3 protein beta/alpha" (SEQ ID No:22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein beta/alpha", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein beta/alpha" nucleic acid or its complement under low stringency conditions,
  - (iii) "14-3-3 protein eta" (SEQ ID No:23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3

protein eta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein eta" nucleic acid or its complement under low stringency conditions,

(iv) "14-3-3 protein gamma" (SEQ ID No:24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein gamma", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein gamma" nucleic acid or its complement under low stringency conditions,

(v) "14-3-3 protein tau" (SEQ ID No:25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein tau", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein tau" nucleic acid or its complement under low stringency conditions,

(vi) "14-3-3 protein zeta/delta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein zeta/delta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein zeta/delta" nucleic acid or its complement under low stringency conditions,

(vii) "ATP-binding cassette, sub-family B, member 7" (SEQ ID No:31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette, sub-family B, member 7", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette, sub-family B, member 7" nucleic acid or its complement under low stringency conditions,

(viii) "ECP-51" (SEQ ID No:32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ECP-51", the variant being encoded by a nucleic acid that hybridizes to the "ECP-51" nucleic acid or its complement under low stringency conditions,

(ix) "GAP-associated tyrosine phosphoprotein p62 " (SEQ ID No:34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "GAP-associated tyrosine phosphoprotein p62 ", the variant being encoded by a nucleic acid that hybridizes to the "GAP-associated tyrosine phosphoprotein p62 " nucleic acid or its complement under low stringency conditions,

(x) "Integral membrane protein 2B (ITM2B) " (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B) ", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B) " nucleic acid or its complement under low stringency conditions,

- (xi) "Krab box protein ensp00000302970" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Krab box protein ensp00000302970", the variant being encoded by a nucleic acid that hybridizes to the "Krab box protein ensp00000302970" nucleic acid or its complement under low stringency conditions,
- (xii) "PDZ domain protein MAGI-3" (SEQ ID No:37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PDZ domain protein MAGI-3", the variant being encoded by a nucleic acid that hybridizes to the "PDZ domain protein MAGI-3" nucleic acid or its complement under low stringency conditions,
- (xiii) "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)" nucleic acid or its complement under low stringency conditions,
- (xiv) "Protein similar to probable mitotic centromere associated kinesin " (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to probable mitotic centromere associated kinesin ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to probable mitotic centromere associated kinesin " nucleic acid or its complement under low stringency conditions,
- (xv) "SAP-62" (SEQ ID No:41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SAP-62", the variant being encoded by a nucleic acid that hybridizes to the "SAP-62" nucleic acid or its complement under low stringency conditions, and
- (xvi) "Zinc finger protein 277" (SEQ ID No:43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Zinc finger protein 277", the variant being encoded by a nucleic acid that hybridizes to the "Zinc finger protein 277" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at

40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. The protein complex according to No. 1 wherein the first protein is the protein "Fe65" (SEQ ID No:33), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid under low stringency conditions.

3. The protein complex according to No. 1 comprising the following proteins:

- (i) "14-3-3 protein epsilon" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein epsilon", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein epsilon" nucleic acid or its complement under low stringency conditions,
- (ii) "14-3-3 protein beta/alpha" (SEQ ID No:22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein beta/alpha", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein beta/alpha" nucleic acid or its complement under low stringency conditions,
- (iii) "14-3-3 protein eta" (SEQ ID No:23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein eta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein eta" nucleic acid or its complement under low stringency conditions,
- (iv) "14-3-3 protein gamma" (SEQ ID No:24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein gamma", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein gamma" nucleic acid or its complement under low stringency conditions,
- (v) "14-3-3 protein tau" (SEQ ID No:25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein tau", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein tau" nucleic acid or its complement under low stringency conditions,
- (vi) "14-3-3 protein zeta/delta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3

protein zeta/delta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein zeta/delta" nucleic acid or its complement under low stringency conditions,

(vii) "APLP1" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP1", the variant being encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(viii) "APLP2" (SEQ ID No:28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP2", the variant being encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(ix) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(x) "APP-C99" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP-C99", the variant being encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(xi) "ATP-binding cassette, sub-family B, member 7" (SEQ ID No:31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette, sub-family B, member 7", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette, sub-family B, member 7" nucleic acid or its complement under low stringency conditions,

(xii) "ECP-51" (SEQ ID No:32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ECP-51", the variant being encoded by a nucleic acid that hybridizes to the "ECP-51" nucleic acid or its complement under low stringency conditions,

(xiii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(xiv) "GAP-associated tyrosine phosphoprotein p62" (SEQ ID No:34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "GAP-associated tyrosine phosphoprotein p62", the variant being

encoded by a nucleic acid that hybridizes to the "GAP-associated tyrosine phosphoprotein p62 " nucleic acid or its complement under low stringency conditions,

(xv) "Integral membrane protein 2B (ITM2B) " (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B) ", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B) " nucleic acid or its complement under low stringency conditions,

(xvi) "Krab box protein ensp00000302970" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Krab box protein ensp00000302970", the variant being encoded by a nucleic acid that hybridizes to the "Krab box protein ensp00000302970" nucleic acid or its complement under low stringency conditions,

(xvii) "PDZ domain protein MAGI-3" (SEQ ID No:37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PDZ domain protein MAGI-3", the variant being encoded by a nucleic acid that hybridizes to the "PDZ domain protein MAGI-3" nucleic acid or its complement under low stringency conditions,

(xviii) "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)" nucleic acid or its complement under low stringency conditions,

(xix) "Protein similar to probable mitotic centromere associated kinesin " (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to probable mitotic centromere associated kinesin ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to probable mitotic centromere associated kinesin " nucleic acid or its complement under low stringency conditions,

(xx) "RNB6" (SEQ ID No:40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RNB6", the variant being encoded by a nucleic acid that hybridizes to the "RNB6" nucleic acid or its complement under low stringency conditions,

(xxi) "SAP-62" (SEQ ID No:41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SAP-62", the variant being encoded by a nucleic acid that hybridizes to the "SAP-62" nucleic acid or its complement under low stringency conditions,

(xxii) "Transcription factor CP2 " (SEQ ID No:42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Transcription factor CP2 ", the variant being encoded by a nucleic acid that hybridizes to the "Transcription factor CP2 " nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "Zinc finger protein 277" (SEQ ID No:43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Zinc finger protein 277", the variant being encoded by a nucleic acid that hybridizes to the "Zinc finger protein 277" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising at least 8 but no more than 22 of the following proteins:

(i) "14-3-3 protein epsilon" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein epsilon", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein epsilon" nucleic acid or its complement under low stringency conditions,

(ii) "14-3-3 protein beta/alpha" (SEQ ID No:22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein beta/alpha", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein beta/alpha" nucleic acid or its complement under low stringency conditions,

(iii) "14-3-3 protein eta" (SEQ ID No:23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein eta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein eta" nucleic acid or its complement under low stringency conditions,

(iv) "14-3-3 protein gamma" (SEQ ID No:24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein gamma", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein gamma" nucleic acid or its complement under low stringency conditions,

- (v) "14-3-3 protein tau" (SEQ ID No:25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein tau", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein tau" nucleic acid or its complement under low stringency conditions,
- (vi) "14-3-3 protein zeta/delta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein zeta/delta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein zeta/delta" nucleic acid or its complement under low stringency conditions,
- (vii) "APLP1" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP1", the variant being encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (viii) "APLP2" (SEQ ID No:28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP2", the variant being encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (ix) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (x) "APP-C99" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP-C99", the variant being encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (xi) "ATP-binding cassette, sub-family B, member 7" (SEQ ID No:31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette, sub-family B, member 7", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette, sub-family B, member 7" nucleic acid or its complement under low stringency conditions,
- (xii) "ECP-51" (SEQ ID No:32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ECP-51", the variant being encoded by a nucleic acid that hybridizes to the "ECP-51" nucleic acid or its complement under low stringency conditions,

- (xiii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (xiv) "GAP-associated tyrosine phosphoprotein p62 " (SEQ ID No:34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "GAP-associated tyrosine phosphoprotein p62 ", the variant being encoded by a nucleic acid that hybridizes to the "GAP-associated tyrosine phosphoprotein p62 " nucleic acid or its complement under low stringency conditions,
- (xv) "Integral membrane protein 2B (ITM2B) " (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B) ", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B) " nucleic acid or its complement under low stringency conditions,
- (xvi) "Krab box protein ensp00000302970" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Krab box protein ensp00000302970", the variant being encoded by a nucleic acid that hybridizes to the "Krab box protein ensp00000302970" nucleic acid or its complement under low stringency conditions,
- (xvii) "PDZ domain protein MAGI-3" (SEQ ID No:37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PDZ domain protein MAGI-3", the variant being encoded by a nucleic acid that hybridizes to the "PDZ domain protein MAGI-3" nucleic acid or its complement under low stringency conditions,
- (xviii) "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)" nucleic acid or its complement under low stringency conditions,
- (xix) "Protein similar to probable mitotic centromere associated kinesin " (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to probable mitotic centromere associated kinesin ", the variant being encoded by a nucleic acid that hybridizes to the

"Protein similar to probable mitotic centromere associated kinesin " nucleic acid or its complement under low stringency conditions,

(xx) "RNB6" (SEQ ID No:40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RNB6", the variant being encoded by a nucleic acid that hybridizes to the "RNB6" nucleic acid or its complement under low stringency conditions,

(xxi) "SAP-62" (SEQ ID No:41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SAP-62", the variant being encoded by a nucleic acid that hybridizes to the "SAP-62" nucleic acid or its complement under low stringency conditions,

(xxii) "Transcription factor CP2 " (SEQ ID No:42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Transcription factor CP2 ", the variant being encoded by a nucleic acid that hybridizes to the "Transcription factor CP2 " nucleic acid or its complement under low stringency conditions,

(xxiii) "Zinc finger protein 277" (SEQ ID No:43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Zinc finger protein 277", the variant being encoded by a nucleic acid that hybridizes to the "Zinc finger protein 277" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the regulation of APP processing and APP function.

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:

expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the Fe65 complex selected from:

(i) "Krab box protein ensp00000302970" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Krab box protein ensp00000302970", the variant being encoded by a nucleic acid that hybridizes to the "Krab box protein ensp00000302970" nucleic acid or its complement under low stringency conditions,

(ii) "Protein similar to probable mitotic centromere associated kinesin " (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to probable mitotic centromere associated kinesin ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to probable mitotic centromere associated kinesin " nucleic acid or its complement under low stringency conditions, and

(iii) "Zinc finger protein 277" (SEQ ID No:43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Zinc finger protein 277", the variant being encoded by a nucleic acid that hybridizes to the "Zinc

finger protein 277" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising:

- (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
- (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b) or
- (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 -

8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container:

- (a) the complex of any of No. 1 – 8 and/or the proteins of No. 13 and/or
- (b) an antibody according to No. 17 and/or
- (c) a nucleic acid encoding a protein of the complex of any of No. 1 – 8 and/or a protein of No. 13 and/or
- (d) cells expressing the complex of any of No. 1 – 8 and/or a protein of No. 13 and, optionally,
- (e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; inflammatory diseases such as chronic inflammatory disorders, rheumatoid arthritis and inflammatory bowel disease; cancer such as prostate cancer and breast cancer and skin cancer .

21. Array, preferably a microarray, in which at least a complex according to any of No. 1 – 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for modifying a physiological substrate of the complex comprising the step of bringing into contact a complex of any of No. 1 – 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 – 8 and/or any of the following the proteins:

- (i) "Krab box protein ensp00000302970" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Krab box protein ensp00000302970", the variant being encoded by a nucleic

acid that hybridizes to the "Krab box protein ensp00000302970" nucleic acid or its complement under low stringency conditions,

(ii) "Protein similar to probable mitotic centromere associated kinesin " (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to probable mitotic centromere associated kinesin ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to probable mitotic centromere associated kinesin " nucleic acid or its complement under low stringency conditions, and/or

(iii) "Zinc finger protein 277" (SEQ ID No:43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Zinc finger protein 277", the variant being encoded by a nucleic acid that hybridizes to the "Zinc finger protein 277" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as a neurodegenerative disease such as Alzheimer's disease; inflammatory diseases such as chronic inflammatory disorders, rheumatoid arthritis and inflammatory bowel disease; cancer such as prostate cancer and breast cancer and skin cancer .

25. A method for screening for a molecule that binds to a complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "Krab box protein ensp00000302970" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Krab box protein ensp00000302970", the variant being encoded by a nucleic acid that hybridizes to the "Krab box protein ensp00000302970" nucleic acid or its complement under low stringency conditions,

(ii) "Protein similar to probable mitotic centromere associated kinesin " (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to probable mitotic centromere associated kinesin ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to probable mitotic centromere associated kinesin " nucleic acid or its complement under low stringency conditions, and/or

(iii) "Zinc finger protein 277" (SEQ ID No:43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Zinc finger protein 277", the variant being encoded by a nucleic acid that hybridizes to the "Zinc finger protein 277" nucleic acid or its complement under low stringency conditions, comprising the steps of:

- (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and
- (b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:

- (a) exposing said complex, or a cell or organism containing Fe65 complex to one or more candidate molecules; and
- (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of

said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether

- (i) "14-3-3 protein epsilon" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein epsilon", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein epsilon" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "14-3-3 protein beta/alpha" (SEQ ID No:22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein beta/alpha", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein beta/alpha" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "14-3-3 protein eta" (SEQ ID No:23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein eta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein eta" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "14-3-3 protein gamma" (SEQ ID No:24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein gamma", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein gamma" nucleic acid or its complement under low stringency conditions, and/or
- (v) "14-3-3 protein tau" (SEQ ID No:25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein tau", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein tau" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "14-3-3 protein zeta/delta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein zeta/delta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein zeta/delta" nucleic acid or its complement under low stringency conditions, and/or

- (vii) "APLP1" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP1", the variant being encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "APLP2" (SEQ ID No:28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP2", the variant being encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (x) "APP-C99" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP-C99", the variant being encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "ATP-binding cassette, sub-family B, member 7" (SEQ ID No:31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette, sub-family B, member 7", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette, sub-family B, member 7" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "ECP-51" (SEQ ID No:32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ECP-51", the variant being encoded by a nucleic acid that hybridizes to the "ECP-51" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "GAP-associated tyrosine phosphoprotein p62 " (SEQ ID No:34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "GAP-associated tyrosine phosphoprotein p62 ", the variant being encoded by a nucleic acid that hybridizes to the "GAP-associated tyrosine

phosphoprotein p62 " nucleic acid or its complement under low stringency conditions, and/or

(xv) "Integral membrane protein 2B (ITM2B) " (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B) ", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B) " nucleic acid or its complement under low stringency conditions, and/or

(xvi) "Krab box protein ensp00000302970" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Krab box protein ensp00000302970", the variant being encoded by a nucleic acid that hybridizes to the "Krab box protein ensp00000302970" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "PDZ domain protein MAGI-3" (SEQ ID No:37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PDZ domain protein MAGI-3", the variant being encoded by a nucleic acid that hybridizes to the "PDZ domain protein MAGI-3" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)" nucleic acid or its complement under low stringency conditions, and/or

(xix) "Protein similar to probable mitotic centromere associated kinesin " (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to probable mitotic centromere associated kinesin ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to probable mitotic centromere associated kinesin " nucleic acid or its complement under low stringency conditions, and/or

(xx) "RNB6" (SEQ ID No:40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RNB6", the variant being encoded by a nucleic acid that hybridizes to the "RNB6" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "SAP-62" (SEQ ID No:41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SAP-62", the variant being encoded by a nucleic acid that hybridizes to the "SAP-62" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "Transcription factor CP2 " (SEQ ID No:42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Transcription factor CP2 ", the variant being encoded by a nucleic acid that hybridizes to the "Transcription factor CP2 " nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "Zinc finger protein 277" (SEQ ID No:43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Zinc finger protein 277", the variant being encoded by a nucleic acid that hybridizes to the "Zinc finger protein 277" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; inflammatory diseases such as chronic inflammatory disorders, rheumatoid arthritis and inflammatory bowel disease; cancer such as prostate cancer and breast cancer and skin cancer .

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; inflammatory diseases such as chronic inflammatory disorders, rheumatoid arthritis and inflammatory bowel disease; cancer such as prostate cancer and breast cancer and skin cancer.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether (i) "14-3-3 protein epsilon" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein epsilon", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein epsilon" nucleic acid or its complement under low stringency conditions, and/or (ii) "14-3-3 protein beta/alpha" (SEQ ID No:22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3

protein beta/alpha", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein beta/alpha" nucleic acid or its complement under low stringency conditions, and/or

(iii) "14-3-3 protein eta" (SEQ ID No:23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein eta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein eta" nucleic acid or its complement under low stringency conditions, and/or

(iv) "14-3-3 protein gamma" (SEQ ID No:24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein gamma", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein gamma" nucleic acid or its complement under low stringency conditions, and/or

(v) "14-3-3 protein tau" (SEQ ID No:25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein tau", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein tau" nucleic acid or its complement under low stringency conditions, and/or

(vi) "14-3-3 protein zeta/delta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein zeta/delta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein zeta/delta" nucleic acid or its complement under low stringency conditions, and/or

(vii) "APLP1" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP1", the variant being encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or

(viii) "APLP2" (SEQ ID No:28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP2", the variant being encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or

(ix) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(x) "APP-C99" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP-C99", the variant

- being encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "ATP-binding cassette, sub-family B, member 7" (SEQ ID No:31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette, sub-family B, member 7", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette, sub-family B, member 7" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "ECP-51" (SEQ ID No:32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ECP-51", the variant being encoded by a nucleic acid that hybridizes to the "ECP-51" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "GAP-associated tyrosine phosphoprotein p62 " (SEQ ID No:34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "GAP-associated tyrosine phosphoprotein p62 ", the variant being encoded by a nucleic acid that hybridizes to the "GAP-associated tyrosine phosphoprotein p62 " nucleic acid or its complement under low stringency conditions, and/or
- (xv) "Integral membrane protein 2B (ITM2B) " (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B) ", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B) " nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "Krab box protein ensp00000302970" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Krab box protein ensp00000302970", the variant being encoded by a nucleic acid that hybridizes to the "Krab box protein ensp00000302970" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "PDZ domain protein MAGI-3" (SEQ ID No:37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PDZ domain protein MAGI-3", the variant being encoded by a nucleic acid that

hybridizes to the "PDZ domain protein MAGI-3" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)" nucleic acid or its complement under low stringency conditions, and/or

(xix) "Protein similar to probable mitotic centromere associated kinesin " (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to probable mitotic centromere associated kinesin ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to probable mitotic centromere associated kinesin " nucleic acid or its complement under low stringency conditions, and/or

(xx) "RNB6" (SEQ ID No:40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RNB6", the variant being encoded by a nucleic acid that hybridizes to the "RNB6" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "SAP-62" (SEQ ID No:41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SAP-62", the variant being encoded by a nucleic acid that hybridizes to the "SAP-62" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "Transcription factor CP2 " (SEQ ID No:42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Transcription factor CP2 ", the variant being encoded by a nucleic acid that hybridizes to the "Transcription factor CP2 " nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "Zinc finger protein 277" (SEQ ID No:43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Zinc finger protein 277", the variant being encoded by a nucleic acid that hybridizes to the "Zinc finger protein 277" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease; inflammatory diseases such as chronic inflammatory disorders, rheumatoid arthritis and inflammatory bowel disease; cancer such as prostate cancer and breast cancer and skin cancer.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the regulation of APP processing and APP function of, or protein composition of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins:

- (i) "14-3-3 protein epsilon" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein epsilon", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein epsilon" nucleic acid or its complement under low stringency conditions,
- (ii) "14-3-3 protein beta/alpha" (SEQ ID No:22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein beta/alpha", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein beta/alpha" nucleic acid or its complement under low stringency conditions,
- (iii) "14-3-3 protein eta" (SEQ ID No:23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein eta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein eta" nucleic acid or its complement under low stringency conditions,

- (iv) "14-3-3 protein gamma" (SEQ ID No:24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein gamma", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein gamma" nucleic acid or its complement under low stringency conditions,
- (v) "14-3-3 protein tau" (SEQ ID No:25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein tau", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein tau" nucleic acid or its complement under low stringency conditions,
- (vi) "14-3-3 protein zeta/delta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein zeta/delta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein zeta/delta" nucleic acid or its complement under low stringency conditions,
- (vii) "APLP1" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP1", the variant being encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (viii) "APLP2" (SEQ ID No:28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP2", the variant being encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (ix) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (x) "APP-C99" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP-C99", the variant being encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (xi) "ATP-binding cassette, sub-family B, member 7" (SEQ ID No:31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette, sub-family B, member 7", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette, sub-family B, member 7" nucleic acid or its complement under low stringency conditions,

- (xii) "ECP-51" (SEQ ID No:32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ECP-51", the variant being encoded by a nucleic acid that hybridizes to the "ECP-51" nucleic acid or its complement under low stringency conditions,
- (xiii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (xiv) "GAP-associated tyrosine phosphoprotein p62 " (SEQ ID No:34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "GAP-associated tyrosine phosphoprotein p62 ", the variant being encoded by a nucleic acid that hybridizes to the "GAP-associated tyrosine phosphoprotein p62 " nucleic acid or its complement under low stringency conditions,
- (xv) "Integral membrane protein 2B (ITM2B) " (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B) ", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B) " nucleic acid or its complement under low stringency conditions,
- (xvi) "Krab box protein ensp00000302970" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Krab box protein ensp00000302970", the variant being encoded by a nucleic acid that hybridizes to the "Krab box protein ensp00000302970" nucleic acid or its complement under low stringency conditions,
- (xvii) "PDZ domain protein MAGI-3" (SEQ ID No:37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PDZ domain protein MAGI-3", the variant being encoded by a nucleic acid that hybridizes to the "PDZ domain protein MAGI-3" nucleic acid or its complement under low stringency conditions,
- (xviii) "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)" nucleic acid or its complement under low stringency conditions,

(xix) "Protein similar to probable mitotic centromere associated kinesin " (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to probable mitotic centromere associated kinesin ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to probable mitotic centromere associated kinesin " nucleic acid or its complement under low stringency conditions,

(xx) "RNB6" (SEQ ID No:40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RNB6", the variant being encoded by a nucleic acid that hybridizes to the "RNB6" nucleic acid or its complement under low stringency conditions,

(xxi) "SAP-62" (SEQ ID No:41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SAP-62", the variant being encoded by a nucleic acid that hybridizes to the "SAP-62" nucleic acid or its complement under low stringency conditions,

(xxii) "Transcription factor CP2 " (SEQ ID No:42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Transcription factor CP2 ", the variant being encoded by a nucleic acid that hybridizes to the "Transcription factor CP2 " nucleic acid or its complement under low stringency conditions, and/or (xxiii) "Zinc finger protein 277" (SEQ ID No:43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Zinc finger protein 277", the variant being encoded by a nucleic acid that hybridizes to the "Zinc finger protein 277" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease; inflammatory diseases such as chronic inflammatory disorders, rheumatoid arthritis and inflammatory bowel disease; cancer such as prostate cancer and breast cancer and skin cancer.

The invention further relates to the X11beta complex:

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein selected from the group consisting of:

- (i) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
  - (ii) "Munc18-1" (SEQ ID No:75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Munc18-1", the variant being encoded by a nucleic acid that hybridizes to the "Munc18-1" nucleic acid or its complement under low stringency conditions,
  - (iii) "Neurexin-1" (SEQ ID No:79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurexin-1", the variant being encoded by a nucleic acid that hybridizes to the "Neurexin-1" nucleic acid or its complement under low stringency conditions,
  - (iv) "Syntaxin-1" (SEQ ID No:93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Syntaxin-1", the variant being encoded by a nucleic acid that hybridizes to the "Syntaxin-1" nucleic acid or its complement under low stringency conditions, and
  - (v) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and
- (b) at least one second protein, which second protein is selected from the group consisting of:
- (i) "ADAMTS-19" (SEQ ID No:44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADAMTS-19", the variant being encoded by a nucleic acid that hybridizes to the "ADAMTS-19" nucleic acid or its complement under low stringency conditions,
  - (ii) "APLP1" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP1", the variant being encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
  - (iii) "Axonemal dynein heavy chain 8" (SEQ ID No:45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Axonemal dynein heavy chain 8", the variant being encoded by a nucleic acid that

hybridizes to the "Axonemal dynein heavy chain 8" nucleic acid or its complement under low stringency conditions,

(iv) "Cadherin EGF LAG seven-pass G-type receptor 2 " (SEQ ID No:46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2 " nucleic acid or its complement under low stringency conditions,

(v) "Calsyntenin-1" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-1", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-1" nucleic acid or its complement under low stringency conditions,

(vi) "Calsyntenin-2" (SEQ ID No:48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-2", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-2" nucleic acid or its complement under low stringency conditions,

(vii) "Calsyntenin-3" (SEQ ID No:49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-3", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-3" nucleic acid or its complement under low stringency conditions,

(viii) "Chondroitin sulfate proteoglycan 6 " (SEQ ID No:50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Chondroitin sulfate proteoglycan 6 ", the variant being encoded by a nucleic acid that hybridizes to the "Chondroitin sulfate proteoglycan 6 " nucleic acid or its complement under low stringency conditions,

(ix) "Chromatin-specific transcription elongation factor FACT 140 kDa subunit" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Chromatin-specific transcription elongation factor FACT 140 kDa subunit", the variant being encoded by a nucleic acid that hybridizes to the "Chromatin-specific transcription elongation factor FACT 140 kDa subunit" nucleic acid or its complement under low stringency conditions,

(x) "DC6 protein" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DC6 protein", the variant being encoded by a nucleic acid that hybridizes to the "DC6 protein" nucleic acid or its complement under low stringency conditions,

- (xi) "Dynein light chain 2A " (SEQ ID No:53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynein light chain 2A ", the variant being encoded by a nucleic acid that hybridizes to the "Dynein light chain 2A " nucleic acid or its complement under low stringency conditions,
- (xii) "Dynein light chain-A " (SEQ ID No:54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynein light chain-A ", the variant being encoded by a nucleic acid that hybridizes to the "Dynein light chain-A " nucleic acid or its complement under low stringency conditions,
- (xiii) "ENG00000168820 (hypothetical protein with p-loop)" (SEQ ID No:55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENG00000168820 (hypothetical protein with p-loop)", the variant being encoded by a nucleic acid that hybridizes to the "ENG00000168820 (hypothetical protein with p-loop)" nucleic acid or its complement under low stringency conditions,
- (xiv) "Eukaryotic translation initiation factor 4A, isoform " (SEQ ID No:56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Eukaryotic translation initiation factor 4A, isoform ", the variant being encoded by a nucleic acid that hybridizes to the "Eukaryotic translation initiation factor 4A, isoform " nucleic acid or its complement under low stringency conditions,
- (xv) "FLJ13910" (SEQ ID No:57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13910", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13910" nucleic acid or its complement under low stringency conditions,
- (xvi) "FRAP1" (SEQ ID No:58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FRAP1", the variant being encoded by a nucleic acid that hybridizes to the "FRAP1" nucleic acid or its complement under low stringency conditions,
- (xvii) "GTP-binding protein ERA" (SEQ ID No:59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "GTP-binding protein ERA", the variant being encoded by a nucleic acid that hybridizes to the "GTP-binding protein ERA" nucleic acid or its complement under low stringency conditions,
- (xviii) "HDAC2" (SEQ ID No:60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HDAC2", the

variant being encoded by a nucleic acid that hybridizes to the "HDAC2" nucleic acid or its complement under low stringency conditions,

(xix) "HERC2 protein" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HERC2 protein", the variant being encoded by a nucleic acid that hybridizes to the "HERC2 protein" nucleic acid or its complement under low stringency conditions,

(xx) "HSPC154" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC154", the variant being encoded by a nucleic acid that hybridizes to the "HSPC154" nucleic acid or its complement under low stringency conditions,

(xxi) "HSPC245" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC245", the variant being encoded by a nucleic acid that hybridizes to the "HSPC245" nucleic acid or its complement under low stringency conditions,

(xxii) "IKAP" (SEQ ID No:64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "IKAP", the variant being encoded by a nucleic acid that hybridizes to the "IKAP" nucleic acid or its complement under low stringency conditions,

(xxiii) "Insulinoma-glucagonoma protein 20" (SEQ ID No:65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Insulinoma-glucagonoma protein 20", the variant being encoded by a nucleic acid that hybridizes to the "Insulinoma-glucagonoma protein 20" nucleic acid or its complement under low stringency conditions,

(xxiv) "KIAA0056" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0056", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0056" nucleic acid or its complement under low stringency conditions,

(xxv) "KIAA0166" (SEQ ID No:67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0166", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0166" nucleic acid or its complement under low stringency conditions,

(xxvi) "KIAA0325" (SEQ ID No:68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0325",

the variant being encoded by a nucleic acid that hybridizes to the "KIAA0325" nucleic acid or its complement under low stringency conditions,

(xxvii) "KIAA0564" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0564", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0564" nucleic acid or its complement under low stringency conditions,

(xxviii) "KIAA0763" (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0763", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0763" nucleic acid or its complement under low stringency conditions,

(xxix) "LIB ( leucine-rich repeat protein)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "LIB ( leucine-rich repeat protein)", the variant being encoded by a nucleic acid that hybridizes to the "LIB ( leucine-rich repeat protein)" nucleic acid or its complement under low stringency conditions,

(xxx) "Laminin, gamma 1 " (SEQ ID No:72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Laminin, gamma 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions,

(xxxi) "MBIP" (SEQ ID No:73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MBIP", the variant being encoded by a nucleic acid that hybridizes to the "MBIP" nucleic acid or its complement under low stringency conditions,

(xxxii) "MEGF7" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEGF7", the variant being encoded by a nucleic acid that hybridizes to the "MEGF7" nucleic acid or its complement under low stringency conditions,

(xxxiii) "Myosin IXB" (SEQ ID No:76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Myosin IXB", the variant being encoded by a nucleic acid that hybridizes to the "Myosin IXB" nucleic acid or its complement under low stringency conditions,

(xxxiv) "NIPSNAP1" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NIPSNAP1",

the variant being encoded by a nucleic acid that hybridizes to the "NIPSNAP1" nucleic acid or its complement under low stringency conditions,

(xxxv) "NIPSNAP2" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NIPSNAP2", the variant being encoded by a nucleic acid that hybridizes to the "NIPSNAP2" nucleic acid or its complement under low stringency conditions,

(xxxvi) "PDZ and LIM domain protein 1" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PDZ and LIM domain protein 1", the variant being encoded by a nucleic acid that hybridizes to the "PDZ and LIM domain protein 1" nucleic acid or its complement under low stringency conditions,

(xxxvii) "PILT" (SEQ ID No:81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PILT", the variant being encoded by a nucleic acid that hybridizes to the "PILT" nucleic acid or its complement under low stringency conditions,

(xxxviii) "Paladin" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Paladin", the variant being encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xxxix) "Peroxisome oxidoreductase 4" (SEQ ID No:83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Peroxisome oxidoreductase 4", the variant being encoded by a nucleic acid that hybridizes to the "Peroxisome oxidoreductase 4" nucleic acid or its complement under low stringency conditions,

(xl) "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)" (SEQ ID No:84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)", the variant being encoded by a nucleic acid that hybridizes to the "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)" nucleic acid or its complement under low stringency conditions,

(xli) "Procollagen C-endopeptidase enhancer " (SEQ ID No:85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Procollagen C-endopeptidase enhancer ", the variant being encoded by a nucleic acid that hybridizes to the "Procollagen C-endopeptidase enhancer " nucleic acid or its complement under low stringency conditions,

(xlii) "Programmed cell death 10" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Programmed cell death 10", the variant being encoded by a nucleic acid that hybridizes to the "Programmed cell death 10" nucleic acid or its complement under low stringency conditions,

(xliii) "Protein similar to AGCP6688 " (SEQ ID No:87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to AGCP6688 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to AGCP6688 " nucleic acid or its complement under low stringency conditions,

(xliv) "RPGR-interacting protein 1" (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RPGR-interacting protein 1", the variant being encoded by a nucleic acid that hybridizes to the "RPGR-interacting protein 1" nucleic acid or its complement under low stringency conditions,

(xlv) "Reelin" (SEQ ID No:89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Reelin", the variant being encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,

(xlvi) "Serine/threonine protein phosphatase 6 " (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Serine/threonine protein phosphatase 6 ", the variant being encoded by a nucleic acid that hybridizes to the "Serine/threonine protein phosphatase 6 " nucleic acid or its complement under low stringency conditions,

(xlvii) "Sortilin-related receptor " (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin-related receptor ", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin-related receptor " nucleic acid or its complement under low stringency conditions,

(xlviii) "Synaptogyrin 3" (SEQ ID No:92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Synaptogyrin 3", the variant being encoded by a nucleic acid that hybridizes to the "Synaptogyrin 3" nucleic acid or its complement under low stringency conditions,

(xlix) "Ubiquitin-protein ligase E3-alpha " (SEQ ID No:94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquitin-protein ligase E3-alpha ", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquitin-protein ligase E3-alpha " nucleic acid or its complement under low stringency conditions,

(l) "VGF nerve growth factor inducible protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "VGF nerve growth factor inducible protein", the variant being encoded by a nucleic acid that hybridizes to the "VGF nerve growth factor inducible protein" nucleic acid or its complement under low stringency conditions, and

(li) "Zinc finger protein 198 " (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Zinc finger protein 198 ", the variant being encoded by a nucleic acid that hybridizes to the "Zinc finger protein 198 " nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. The protein complex according to No. 1 wherein the first protein is the protein "X11beta" (SEQ ID No:96), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid under low stringency conditions.

3. The protein complex according to No. 1 comprising the following proteins:

(i) "ADAMTS-19" (SEQ ID No:44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADAMTS-19", the variant being encoded by a nucleic acid that hybridizes to the "ADAMTS-19" nucleic acid or its complement under low stringency conditions,

- (ii) "APLP1" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP1", the variant being encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (iii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "Axonemal dynein heavy chain 8" (SEQ ID No:45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Axonemal dynein heavy chain 8", the variant being encoded by a nucleic acid that hybridizes to the "Axonemal dynein heavy chain 8" nucleic acid or its complement under low stringency conditions,
- (v) "Cadherin EGF LAG seven-pass G-type receptor 2 " (SEQ ID No:46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2 " nucleic acid or its complement under low stringency conditions,
- (vi) "Calsyntenin-1" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-1", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-1" nucleic acid or its complement under low stringency conditions,
- (vii) "Calsyntenin-2" (SEQ ID No:48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-2", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-2" nucleic acid or its complement under low stringency conditions,
- (viii) "Calsyntenin-3" (SEQ ID No:49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-3", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-3" nucleic acid or its complement under low stringency conditions,
- (ix) "Chondroitin sulfate proteoglycan 6 " (SEQ ID No:50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Chondroitin sulfate proteoglycan 6 ", the variant being encoded by a nucleic

acid that hybridizes to the "Chondroitin sulfate proteoglycan 6 " nucleic acid or its complement under low stringency conditions,

(x) "Chromatin-specific transcription elongation factor FACT 140 kDa subunit" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Chromatin-specific transcription elongation factor FACT 140 kDa subunit", the variant being encoded by a nucleic acid that hybridizes to the "Chromatin-specific transcription elongation factor FACT 140 kDa subunit" nucleic acid or its complement under low stringency conditions,

(xi) "DC6 protein" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DC6 protein", the variant being encoded by a nucleic acid that hybridizes to the "DC6 protein" nucleic acid or its complement under low stringency conditions,

(xii) "Dynein light chain 2A " (SEQ ID No:53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynein light chain 2A ", the variant being encoded by a nucleic acid that hybridizes to the "Dynein light chain 2A " nucleic acid or its complement under low stringency conditions,

(xiii) "Dynein light chain-A " (SEQ ID No:54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynein light chain-A ", the variant being encoded by a nucleic acid that hybridizes to the "Dynein light chain-A " nucleic acid or its complement under low stringency conditions,

(xiv) "ENG00000168820 (hypothetical protein with p-loop)" (SEQ ID No:55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENG00000168820 (hypothetical protein with p-loop)", the variant being encoded by a nucleic acid that hybridizes to the "ENG00000168820 (hypothetical protein with p-loop)" nucleic acid or its complement under low stringency conditions,

(xv) "Eukaryotic translation initiation factor 4A, isoform " (SEQ ID No:56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Eukaryotic translation initiation factor 4A, isoform ", the variant being encoded by a nucleic acid that hybridizes to the "Eukaryotic translation initiation factor 4A, isoform " nucleic acid or its complement under low stringency conditions,

(xvi) "FLJ13910" (SEQ ID No:57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13910",

the variant being encoded by a nucleic acid that hybridizes to the "FLJ13910" nucleic acid or its complement under low stringency conditions,

(xvii) "FRAP1" (SEQ ID No:58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FRAP1", the variant being encoded by a nucleic acid that hybridizes to the "FRAP1" nucleic acid or its complement under low stringency conditions,

(xviii) "GTP-binding protein ERA" (SEQ ID No:59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "GTP-binding protein ERA", the variant being encoded by a nucleic acid that hybridizes to the "GTP-binding protein ERA" nucleic acid or its complement under low stringency conditions,

(xix) "HDAC2" (SEQ ID No:60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HDAC2", the variant being encoded by a nucleic acid that hybridizes to the "HDAC2" nucleic acid or its complement under low stringency conditions,

(xx) "HERC2 protein" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HERC2 protein", the variant being encoded by a nucleic acid that hybridizes to the "HERC2 protein" nucleic acid or its complement under low stringency conditions,

(xxi) "HSPC154" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC154", the variant being encoded by a nucleic acid that hybridizes to the "HSPC154" nucleic acid or its complement under low stringency conditions,

(xxii) "HSPC245" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC245", the variant being encoded by a nucleic acid that hybridizes to the "HSPC245" nucleic acid or its complement under low stringency conditions,

(xxiii) "IKAP" (SEQ ID No:64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "IKAP", the variant being encoded by a nucleic acid that hybridizes to the "IKAP" nucleic acid or its complement under low stringency conditions,

(xxiv) "Insulinoma-glucagonoma protein 20" (SEQ ID No:65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Insulinoma-glucagonoma protein 20", the variant being encoded by a nucleic

acid that hybridizes to the "Insulinoma-glucagonoma protein 20" nucleic acid or its complement under low stringency conditions,

(xxv) "KIAA0056" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0056", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0056" nucleic acid or its complement under low stringency conditions,

(xxvi) "KIAA0166" (SEQ ID No:67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0166", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0166" nucleic acid or its complement under low stringency conditions,

(xxvii) "KIAA0325" (SEQ ID No:68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0325", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0325" nucleic acid or its complement under low stringency conditions,

(xxviii) "KIAA0564" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0564", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0564" nucleic acid or its complement under low stringency conditions,

(xxix) "KIAA0763" (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0763", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0763" nucleic acid or its complement under low stringency conditions,

(xxx) "LIB ( leucine-rich repeat protein)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "LIB ( leucine-rich repeat protein)", the variant being encoded by a nucleic acid that hybridizes to the "LIB ( leucine-rich repeat protein)" nucleic acid or its complement under low stringency conditions,

(xxxi) "Laminin, gamma 1 " (SEQ ID No:72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Laminin, gamma 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions,

(xxxii) "MBIP" (SEQ ID No:73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MBIP", the variant being

encoded by a nucleic acid that hybridizes to the "MBIP" nucleic acid or its complement under low stringency conditions,

(xxxiii) "MEGF7" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEGF7", the variant being encoded by a nucleic acid that hybridizes to the "MEGF7" nucleic acid or its complement under low stringency conditions,

(xxxiv) "Munc18-1" (SEQ ID No:75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Munc18-1", the variant being encoded by a nucleic acid that hybridizes to the "Munc18-1" nucleic acid or its complement under low stringency conditions,

(xxxv) "Myosin IXB" (SEQ ID No:76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Myosin IXB", the variant being encoded by a nucleic acid that hybridizes to the "Myosin IXB" nucleic acid or its complement under low stringency conditions,

(xxxvi) "NIPSNAP1" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NIPSNAP1", the variant being encoded by a nucleic acid that hybridizes to the "NIPSNAP1" nucleic acid or its complement under low stringency conditions,

(xxxvii) "NIPSNAP2" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NIPSNAP2", the variant being encoded by a nucleic acid that hybridizes to the "NIPSNAP2" nucleic acid or its complement under low stringency conditions,

(xxxviii) "Neurexin-1" (SEQ ID No:79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurexin-1", the variant being encoded by a nucleic acid that hybridizes to the "Neurexin-1" nucleic acid or its complement under low stringency conditions,

(xxxix) "PDZ and LIM domain protein 1" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PDZ and LIM domain protein 1", the variant being encoded by a nucleic acid that hybridizes to the "PDZ and LIM domain protein 1" nucleic acid or its complement under low stringency conditions,

(xi) "PILT" (SEQ ID No:81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PILT", the variant being

encoded by a nucleic acid that hybridizes to the "PILT" nucleic acid or its complement under low stringency conditions,

(xli) "Paladin" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Paladin", the variant being encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xlii) "Peroxisredoxin 4" (SEQ ID No:83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Peroxisredoxin 4", the variant being encoded by a nucleic acid that hybridizes to the "Peroxisredoxin 4" nucleic acid or its complement under low stringency conditions,

(xliii) "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)" (SEQ ID No:84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)", the variant being encoded by a nucleic acid that hybridizes to the "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)" nucleic acid or its complement under low stringency conditions,

(xliv) "Procollagen C-endopeptidase enhancer " (SEQ ID No:85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Procollagen C-endopeptidase enhancer ", the variant being encoded by a nucleic acid that hybridizes to the "Procollagen C-endopeptidase enhancer " nucleic acid or its complement under low stringency conditions,

(xlv) "Programmed cell death 10" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Programmed cell death 10", the variant being encoded by a nucleic acid that hybridizes to the "Programmed cell death 10" nucleic acid or its complement under low stringency conditions,

(xlvii) "Protein similar to AGCP6688 " (SEQ ID No:87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to AGCP6688 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to AGCP6688 " nucleic acid or its complement under low stringency conditions,

(xlviii) "RPGR-interacting protein 1" (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RPGR-interacting protein 1", the variant being encoded by a nucleic acid that hybridizes

to the "RPGR-interacting protein 1" nucleic acid or its complement under low stringency conditions,

(xlviii) "Reelin" (SEQ ID No:89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Reelin", the variant being encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,

(xlix) "Serine/threonine protein phosphatase 6 " (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Serine/threonine protein phosphatase 6 ", the variant being encoded by a nucleic acid that hybridizes to the "Serine/threonine protein phosphatase 6 " nucleic acid or its complement under low stringency conditions,

(i) "Sortilin-related receptor " (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin-related receptor ", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin-related receptor " nucleic acid or its complement under low stringency conditions,

(ii) "Synaptogyrin 3" (SEQ ID No:92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Synaptogyrin 3", the variant being encoded by a nucleic acid that hybridizes to the "Synaptogyrin 3" nucleic acid or its complement under low stringency conditions,

(lii) "Syntaxin-1" (SEQ ID No:93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Syntaxin-1", the variant being encoded by a nucleic acid that hybridizes to the "Syntaxin-1" nucleic acid or its complement under low stringency conditions,

(liii) "Ubiquitin-protein ligase E3-alpha " (SEQ ID No:94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquitin-protein ligase E3-alpha ", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquitin-protein ligase E3-alpha " nucleic acid or its complement under low stringency conditions,

(liv) "VGF nerve growth factor inducible protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "VGF nerve growth factor inducible protein", the variant being encoded by a nucleic acid that hybridizes to the "VGF nerve growth factor inducible protein" nucleic acid or its complement under low stringency conditions,

(iv) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and/or

(vi) "Zinc finger protein 198 " (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Zinc finger protein 198 ", the variant being encoded by a nucleic acid that hybridizes to the "Zinc finger protein 198 " nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising at least 6 but no more than 56 of the following proteins:

(i) "ADAMTS-19" (SEQ ID No:44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADAMTS-19", the variant being encoded by a nucleic acid that hybridizes to the "ADAMTS-19" nucleic acid or its complement under low stringency conditions,

(ii) "APLP1" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP1", the variant being encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "Axonemal dynein heavy chain 8" (SEQ ID No:45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Axonemal dynein heavy chain 8", the variant being encoded by a nucleic acid that hybridizes to the "Axonemal dynein heavy chain 8" nucleic acid or its complement under low stringency conditions,

(v) "Cadherin EGF LAG seven-pass G-type receptor 2 " (SEQ ID No:46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2 " nucleic acid or its complement under low stringency conditions,

- (vi) "Calsyntenin-1" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-1", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-1" nucleic acid or its complement under low stringency conditions,
- (vii) "Calsyntenin-2" (SEQ ID No:48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-2", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-2" nucleic acid or its complement under low stringency conditions,
- (viii) "Calsyntenin-3" (SEQ ID No:49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-3", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-3" nucleic acid or its complement under low stringency conditions,
- (ix) "Chondroitin sulfate proteoglycan 6 " (SEQ ID No:50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Chondroitin sulfate proteoglycan 6 ", the variant being encoded by a nucleic acid that hybridizes to the "Chondroitin sulfate proteoglycan 6 " nucleic acid or its complement under low stringency conditions,
- (x) "Chromatin-specific transcription elongation factor FACT 140 kDa subunit" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Chromatin-specific transcription elongation factor FACT 140 kDa subunit", the variant being encoded by a nucleic acid that hybridizes to the "Chromatin-specific transcription elongation factor FACT 140 kDa subunit" nucleic acid or its complement under low stringency conditions,
- (xi) "DC6 protein" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DC6 protein", the variant being encoded by a nucleic acid that hybridizes to the "DC6 protein" nucleic acid or its complement under low stringency conditions,
- (xii) "Dynein light chain 2A " (SEQ ID No:53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynein light chain 2A ", the variant being encoded by a nucleic acid that hybridizes to the "Dynein light chain 2A " nucleic acid or its complement under low stringency conditions,
- (xiii) "Dynein light chain-A " (SEQ ID No:54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynein

light chain-A ", the variant being encoded by a nucleic acid that hybridizes to the "Dynein light chain-A " nucleic acid or its complement under low stringency conditions,

(xiv) "ENG00000168820 (hypothetical protein with p-loop)" (SEQ ID No:55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENG00000168820 (hypothetical protein with p-loop)", the variant being encoded by a nucleic acid that hybridizes to the "ENG00000168820 (hypothetical protein with p-loop)" nucleic acid or its complement under low stringency conditions,

(xv) "Eukaryotic translation initiation factor 4A, isoform " (SEQ ID No:56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Eukaryotic translation initiation factor 4A, isoform ", the variant being encoded by a nucleic acid that hybridizes to the "Eukaryotic translation initiation factor 4A, isoform " nucleic acid or its complement under low stringency conditions,

(xvi) "FLJ13910" (SEQ ID No:57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13910", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13910" nucleic acid or its complement under low stringency conditions,

(xvii) "FRAP1" (SEQ ID No:58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FRAP1", the variant being encoded by a nucleic acid that hybridizes to the "FRAP1" nucleic acid or its complement under low stringency conditions,

(xviii) "GTP-binding protein ERA" (SEQ ID No:59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "GTP-binding protein ERA", the variant being encoded by a nucleic acid that hybridizes to the "GTP-binding protein ERA" nucleic acid or its complement under low stringency conditions,

(xix) "HDAC2" (SEQ ID No:60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HDAC2", the variant being encoded by a nucleic acid that hybridizes to the "HDAC2" nucleic acid or its complement under low stringency conditions,

(xx) "HERC2 protein" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HERC2 protein", the variant being encoded by a nucleic acid that hybridizes to the "HERC2 protein" nucleic acid or its complement under low stringency conditions,

- (xxi) "HSPC154" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC154", the variant being encoded by a nucleic acid that hybridizes to the "HSPC154" nucleic acid or its complement under low stringency conditions,
- (xxii) "HSPC245" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC245", the variant being encoded by a nucleic acid that hybridizes to the "HSPC245" nucleic acid or its complement under low stringency conditions,
- (xxiii) "IKAP" (SEQ ID No:64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "IKAP", the variant being encoded by a nucleic acid that hybridizes to the "IKAP" nucleic acid or its complement under low stringency conditions,
- (xxiv) "Insulinoma-glucagonoma protein 20" (SEQ ID No:65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Insulinoma-glucagonoma protein 20", the variant being encoded by a nucleic acid that hybridizes to the "Insulinoma-glucagonoma protein 20" nucleic acid or its complement under low stringency conditions,
- (xxv) "KIAA0056" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0056", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0056" nucleic acid or its complement under low stringency conditions,
- (xxvi) "KIAA0166" (SEQ ID No:67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0166", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0166" nucleic acid or its complement under low stringency conditions,
- (xxvii) "KIAA0325" (SEQ ID No:68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0325", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0325" nucleic acid or its complement under low stringency conditions,
- (xxviii) "KIAA0564" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0564", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0564" nucleic acid or its complement under low stringency conditions,

(xxix) "KIAA0763" (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0763", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0763" nucleic acid or its complement under low stringency conditions,

(xxx) "LIB ( leucine-rich repeat protein)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "LIB ( leucine-rich repeat protein)", the variant being encoded by a nucleic acid that hybridizes to the "LIB ( leucine-rich repeat protein)" nucleic acid or its complement under low stringency conditions,

(xxxi) "Laminin, gamma 1 " (SEQ ID No:72) or a functionally active derivative thereof; or a functionally active fragment thereof, or a homologue thereof, or a variant of "Laminin, gamma 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions,

(xxxii) "MBIP" (SEQ ID No:73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MBIP", the variant being encoded by a nucleic acid that hybridizes to the "MBIP" nucleic acid or its complement under low stringency conditions,

(xxxiii) "MEGF7" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEGF7", the variant being encoded by a nucleic acid that hybridizes to the "MEGF7" nucleic acid or its complement under low stringency conditions,

(xxxiv) "Munc18-1" (SEQ ID No:75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Munc18-1", the variant being encoded by a nucleic acid that hybridizes to the "Munc18-1" nucleic acid or its complement under low stringency conditions,

(xxxv) "Myosin IXB" (SEQ ID No:76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Myosin IXB", the variant being encoded by a nucleic acid that hybridizes to the "Myosin IXB" nucleic acid or its complement under low stringency conditions,

(xxxvi) "NIPSNAP1" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NIPSNAP1", the variant being encoded by a nucleic acid that hybridizes to the "NIPSNAP1" nucleic acid or its complement under low stringency conditions,

(xxxvii) "NIPSNAP2" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NIPSNAP2", the variant being encoded by a nucleic acid that hybridizes to the "NIPSNAP2" nucleic acid or its complement under low stringency conditions,

(xxxviii) "Neurexin-1" (SEQ ID No:79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurexin-1", the variant being encoded by a nucleic acid that hybridizes to the "Neurexin-1" nucleic acid or its complement under low stringency conditions,

(xxxix) "PDZ and LIM domain protein 1" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PDZ and LIM domain protein 1", the variant being encoded by a nucleic acid that hybridizes to the "PDZ and LIM domain protein 1" nucleic acid or its complement under low stringency conditions,

(xl) "PILT" (SEQ ID No:81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PILT", the variant being encoded by a nucleic acid that hybridizes to the "PILT" nucleic acid or its complement under low stringency conditions,

(xli) "Paladin" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Paladin", the variant being encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xlii) "Peroxisome oxidoreductase 4" (SEQ ID No:83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Peroxisome oxidoreductase 4", the variant being encoded by a nucleic acid that hybridizes to the "Peroxisome oxidoreductase 4" nucleic acid or its complement under low stringency conditions,

(xliii) "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)" (SEQ ID No:84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)", the variant being encoded by a nucleic acid that hybridizes to the "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)" nucleic acid or its complement under low stringency conditions,

(xliv) "Procollagen C-endopeptidase enhancer" (SEQ ID No:85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Procollagen C-endopeptidase enhancer", the variant being encoded by a

nucleic acid that hybridizes to the "Procollagen C-endopeptidase enhancer " nucleic acid or its complement under low stringency conditions,

(xlv) "Programmed cell death 10" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Programmed cell death 10", the variant being encoded by a nucleic acid that hybridizes to the "Programmed cell death 10" nucleic acid or its complement under low stringency conditions,

(xlvi) "Protein similar to AGCP6688 " (SEQ ID No:87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to AGCP6688 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to AGCP6688 " nucleic acid or its complement under low stringency conditions,

(xlvii) "RPGR-interacting protein 1" (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RPGR-interacting protein 1", the variant being encoded by a nucleic acid that hybridizes to the "RPGR-interacting protein 1" nucleic acid or its complement under low stringency conditions,

(xlviii) "Reelin" (SEQ ID No:89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Reelin", the variant being encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,

(xlix) "Serine/threonine protein phosphatase 6 " (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Serine/threonine protein phosphatase 6 ", the variant being encoded by a nucleic acid that hybridizes to the "Serine/threonine protein phosphatase 6 " nucleic acid or its complement under low stringency conditions,

(l) "Sortilin-related receptor " (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin-related receptor ", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin-related receptor " nucleic acid or its complement under low stringency conditions,

(li) "Synaptogyrin 3" (SEQ ID No:92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Synaptogyrin 3", the variant being encoded by a nucleic acid that hybridizes to the "Synaptogyrin 3" nucleic acid or its complement under low stringency conditions,

(lii) "Syntaxin-1" (SEQ ID No:93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Syntaxin-1", the variant being encoded by a nucleic acid that hybridizes to the "Syntaxin-1" nucleic acid or its complement under low stringency conditions,

(liii) "Ubiquitin-protein ligase E3-alpha " (SEQ ID No:94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquitin-protein ligase E3-alpha ", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquitin-protein ligase E3-alpha " nucleic acid or its complement under low stringency conditions,

(liv) "VGF nerve growth factor inducible protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "VGF nerve growth factor inducible protein", the variant being encoded by a nucleic acid that hybridizes to the "VGF nerve growth factor inducible protein" nucleic acid or its complement under low stringency conditions,

(lv) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions,

(lvi) "Zinc finger protein 198 " (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Zinc finger protein 198 ", the variant being encoded by a nucleic acid that hybridizes to the "Zinc finger protein 198 " nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the regulation of APP processing and APP function.

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:

expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the X11beta complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the X11beta complex selected from

(i) "ADAMTS-19" (SEQ ID No:44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADAMTS-19", the variant being encoded by a nucleic acid that hybridizes to the "ADAMTS-19" nucleic acid or its complement under low stringency conditions,

(ii) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,

- (iii) "Calsyntenin-2" (SEQ ID No:48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-2", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-2" nucleic acid or its complement under low stringency conditions,
- (iv) "Calsyntenin-3" (SEQ ID No:49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-3", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-3" nucleic acid or its complement under low stringency conditions,
- (v) "ENG00000168820 (hypothetical protein with p-loop)" (SEQ ID No:55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENG00000168820 (hypothetical protein with p-loop)", the variant being encoded by a nucleic acid that hybridizes to the "ENG00000168820 (hypothetical protein with p-loop)" nucleic acid or its complement under low stringency conditions,
- (vi) "FLJ13910" (SEQ ID No:57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13910", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13910" nucleic acid or its complement under low stringency conditions,
- (vii) "HERC2 protein" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HERC2 protein", the variant being encoded by a nucleic acid that hybridizes to the "HERC2 protein" nucleic acid or its complement under low stringency conditions,
- (viii) "HSPC154" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC154", the variant being encoded by a nucleic acid that hybridizes to the "HSPC154" nucleic acid or its complement under low stringency conditions,
- (ix) "HSPC245" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC245", the variant being encoded by a nucleic acid that hybridizes to the "HSPC245" nucleic acid or its complement under low stringency conditions,
- (x) "KIAA0056" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0056", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0056" nucleic acid or its complement under low stringency conditions,

- (xi) "KIAA0166" (SEQ ID No:67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0166", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0166" nucleic acid or its complement under low stringency conditions,
- (xii) "KIAA0564" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0564", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0564" nucleic acid or its complement under low stringency conditions,
- (xiii) "KIAA0763" (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0763", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0763" nucleic acid or its complement under low stringency conditions,
- (xiv) "MEGF7" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEGF7", the variant being encoded by a nucleic acid that hybridizes to the "MEGF7" nucleic acid or its complement under low stringency conditions,
- (xv) "NIPSNAP1" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NIPSNAP1", the variant being encoded by a nucleic acid that hybridizes to the "NIPSNAP1" nucleic acid or its complement under low stringency conditions,
- (xvi) "PDZ and LIM domain protein 1" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PDZ and LIM domain protein 1", the variant being encoded by a nucleic acid that hybridizes to the "PDZ and LIM domain protein 1" nucleic acid or its complement under low stringency conditions,
- (xvii) "PILT" (SEQ ID No:81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PILT", the variant being encoded by a nucleic acid that hybridizes to the "PILT" nucleic acid or its complement under low stringency conditions,
- (xviii) "Paladin" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Paladin", the variant being encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xix) "Programmed cell death 10" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Programmed cell death 10", the variant being encoded by a nucleic acid that hybridizes to the "Programmed cell death 10" nucleic acid or its complement under low stringency conditions,

(xx) "Protein similar to AGCP6688 " (SEQ ID No:87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to AGCP6688 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to AGCP6688 " nucleic acid or its complement under low stringency conditions, and

(xxi) "Ubiquitin-protein ligase E3-alpha " (SEQ ID No:94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquitin-protein ligase E3-alpha ", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquitin-protein ligase E3-alpha " nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising:

(a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or

(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b) or

(c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container:

- (a) the complex of any of No. 1 – 8 and/or the proteins of No. 13, and/or
- (b) an antibody according to No. 17 and/or
- (c) a nucleic acid encoding a protein of the complex of any of No. 1 – 8 and/or a protein of No. 13 and/or
- (d) cells expressing the complex of any of No. 1 – 8 and/or a protein of No. 13 and, optionally,
- (e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; inflammatory conditions such as ulcerative colitis, Crohn's disease and arteriosclerosis.

21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for modifying a physiological substrate of the complex comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "ADAMTS-19" (SEQ ID No:44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADAMTS-19", the variant being encoded by a nucleic acid that hybridizes to the "ADAMTS-19" nucleic acid or its complement under low stringency conditions,
- (ii) "Cadherin EGF LAG seven-pass G-type receptor 2 " (SEQ ID No:46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2 " nucleic acid or its complement under low stringency conditions,
- (iii) "Calsyntenin-2" (SEQ ID No:48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-2", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-2" nucleic acid or its complement under low stringency conditions,
- (iv) "Calsyntenin-3" (SEQ ID No:49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-3", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-3" nucleic acid or its complement under low stringency conditions,
- (v) "ENG00000168820 (hypothetical protein with p-loop)" (SEQ ID No:55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENG00000168820 (hypothetical protein with p-loop)", the variant being encoded by a nucleic acid that hybridizes to the "ENG00000168820 (hypothetical protein with p-loop)" nucleic acid or its complement under low stringency conditions,

- (vi) "FLJ13910" (SEQ ID No:57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13910", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13910" nucleic acid or its complement under low stringency conditions,
- (vii) "HERC2 protein" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HERC2 protein", the variant being encoded by a nucleic acid that hybridizes to the "HERC2 protein" nucleic acid or its complement under low stringency conditions,
- (viii) "HSPC154" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC154", the variant being encoded by a nucleic acid that hybridizes to the "HSPC154" nucleic acid or its complement under low stringency conditions,
- (ix) "HSPC245" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC245", the variant being encoded by a nucleic acid that hybridizes to the "HSPC245" nucleic acid or its complement under low stringency conditions,
- (x) "KIAA0056" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0056", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0056" nucleic acid or its complement under low stringency conditions,
- (xi) "KIAA0166" (SEQ ID No:67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0166", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0166" nucleic acid or its complement under low stringency conditions,
- (xii) "KIAA0564" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0564", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0564" nucleic acid or its complement under low stringency conditions,
- (xiii) "KIAA0763" (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0763", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0763" nucleic acid or its complement under low stringency conditions,
- (xiv) "MEGF7" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEGF7", the variant

being encoded by a nucleic acid that hybridizes to the "MEGF7" nucleic acid or its complement under low stringency conditions,

(xv) "NIPSNAP1" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NIPSNAP1", the variant being encoded by a nucleic acid that hybridizes to the "NIPSNAP1" nucleic acid or its complement under low stringency conditions,

(xvi) "PDZ and LIM domain protein 1" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PDZ and LIM domain protein 1", the variant being encoded by a nucleic acid that hybridizes to the "PDZ and LIM domain protein 1" nucleic acid or its complement under low stringency conditions,

(xvii) "PILT" (SEQ ID No:81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PILT", the variant being encoded by a nucleic acid that hybridizes to the "PILT" nucleic acid or its complement under low stringency conditions,

(xviii) "Paladin" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Paladin", the variant being encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xix) "Programmed cell death 10" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Programmed cell death 10", the variant being encoded by a nucleic acid that hybridizes to the "Programmed cell death 10" nucleic acid or its complement under low stringency conditions,

(xx) "Protein similar to AGCP6688 " (SEQ ID No:87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to AGCP6688 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to AGCP6688 " nucleic acid or its complement under low stringency conditions, and/or

(xxi) "Ubiquitin-protein ligase E3-alpha " (SEQ ID No:94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquitin-protein ligase E3-alpha ", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquitin-protein ligase E3-alpha " nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as a neurodegenerative disease such as Alzheimer's disease; inflammatory conditions such as ulcerative colitis, Crohn's disease and atherosclerosis.

25. A method for screening for a molecule that binds to a complex of any one of No. 1 - 8 and/or any of the following the proteins:

- (i) "ADAMTS-19" (SEQ ID No:44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADAMTS-19", the variant being encoded by a nucleic acid that hybridizes to the "ADAMTS-19" nucleic acid or its complement under low stringency conditions,
- (ii) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,
- (iii) "Calsyntenin-2" (SEQ ID No:48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-2", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-2" nucleic acid or its complement under low stringency conditions,
- (iv) "Calsyntenin-3" (SEQ ID No:49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-3", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-3" nucleic acid or its complement under low stringency conditions,
- (v) "ENG00000168820 (hypothetical protein with p-loop)" (SEQ ID No:55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENG00000168820 (hypothetical protein with p-loop)", the variant being encoded by a nucleic acid that hybridizes to the "ENG00000168820 (hypothetical protein with p-loop)" nucleic acid or its complement under low stringency conditions,
- (vi) "FLJ13910" (SEQ ID No:57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13910", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13910" nucleic acid or its complement under low stringency conditions,

- (vii) "HERC2 protein" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HERC2 protein", the variant being encoded by a nucleic acid that hybridizes to the "HERC2 protein" nucleic acid or its complement under low stringency conditions,
- (viii) "HSPC154" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC154", the variant being encoded by a nucleic acid that hybridizes to the "HSPC154" nucleic acid or its complement under low stringency conditions,
- (ix) "HSPC245" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC245", the variant being encoded by a nucleic acid that hybridizes to the "HSPC245" nucleic acid or its complement under low stringency conditions,
- (x) "KIAA0056" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0056", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0056" nucleic acid or its complement under low stringency conditions,
- (xi) "KIAA0166" (SEQ ID No:67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0166", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0166" nucleic acid or its complement under low stringency conditions,
- (xii) "KIAA0564" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0564", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0564" nucleic acid or its complement under low stringency conditions,
- (xiii) "KIAA0763" (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0763", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0763" nucleic acid or its complement under low stringency conditions,
- (xiv) "MEGF7" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEGF7", the variant being encoded by a nucleic acid that hybridizes to the "MEGF7" nucleic acid or its complement under low stringency conditions,
- (xv) "NIPSNAP1" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NIPSNAP1",

the variant being encoded by a nucleic acid that hybridizes to the "NIPSNAP1" nucleic acid or its complement under low stringency conditions,

(xvi) "PDZ and LIM domain protein 1" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PDZ and LIM domain protein 1", the variant being encoded by a nucleic acid that hybridizes to the "PDZ and LIM domain protein 1" nucleic acid or its complement under low stringency conditions,

(xvii) "PILT" (SEQ ID No:81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PILT", the variant being encoded by a nucleic acid that hybridizes to the "PILT" nucleic acid or its complement under low stringency conditions,

(xviii) "Paladin" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Paladin", the variant being encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xix) "Programmed cell death 10" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Programmed cell death 10", the variant being encoded by a nucleic acid that hybridizes to the "Programmed cell death 10" nucleic acid or its complement under low stringency conditions,

(xx) "Protein similar to AGCP6688 " (SEQ ID No:87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to AGCP6688 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to AGCP6688 " nucleic acid or its complement under low stringency conditions, and/or

(xxi) "Ubiquitin-protein ligase E3-alpha " (SEQ ID No:94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquitin-protein ligase E3-alpha ", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquitin-protein ligase E3-alpha " nucleic acid or its complement under low stringency conditions, comprising the steps of:

(a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:

- (a) exposing said complex, or a cell or organism containing X11beta complex to one or more candidate molecules; and
- (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether (i) "ADAMTS-19" (SEQ ID No:44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADAMTS-

19", the variant being encoded by a nucleic acid that hybridizes to the "ADAMTS-19" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APLP1" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP1", the variant being encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Axonemal dynein heavy chain 8" (SEQ ID No:45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Axonemal dynein heavy chain 8", the variant being encoded by a nucleic acid that hybridizes to the "Axonemal dynein heavy chain 8" nucleic acid or its complement under low stringency conditions, and/or

(v) "Cadherin EGF LAG seven-pass G-type receptor 2 " (SEQ ID No:46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2 " nucleic acid or its complement under low stringency conditions, and/or

(vi) "Calsyntenin-1" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-1", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-1" nucleic acid or its complement under low stringency conditions, and/or

(vii) "Calsyntenin-2" (SEQ ID No:48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-2", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-2" nucleic acid or its complement under low stringency conditions, and/or

(viii) "Calsyntenin-3" (SEQ ID No:49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-3", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-3" nucleic acid or its complement under low stringency conditions, and/or

- (ix) "Chondroitin sulfate proteoglycan 6 " (SEQ ID No:50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Chondroitin sulfate proteoglycan 6 ", the variant being encoded by a nucleic acid that hybridizes to the "Chondroitin sulfate proteoglycan 6 " nucleic acid or its complement under low stringency conditions, and/or
- (x) "Chromatin-specific transcription elongation factor FACT 140 kDa subunit" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Chromatin-specific transcription elongation factor FACT 140 kDa subunit", the variant being encoded by a nucleic acid that hybridizes to the "Chromatin-specific transcription elongation factor FACT 140 kDa subunit" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "DC6 protein" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DC6 protein", the variant being encoded by a nucleic acid that hybridizes to the "DC6 protein" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "Dynein light chain 2A " (SEQ ID No:53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynein light chain 2A ", the variant being encoded by a nucleic acid that hybridizes to the "Dynein light chain 2A " nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "Dynein light chain-A " (SEQ ID No:54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynein light chain-A ", the variant being encoded by a nucleic acid that hybridizes to the "Dynein light chain-A " nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "ENG00000168820 (hypothetical protein with p-loop)" (SEQ ID No:55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENG00000168820 (hypothetical protein with p-loop)", the variant being encoded by a nucleic acid that hybridizes to the "ENG00000168820 (hypothetical protein with p-loop)" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "Eukaryotic translation initiation factor 4A, isoform " (SEQ ID No:56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Eukaryotic translation initiation factor 4A, isoform ", the variant being encoded by a nucleic acid that hybridizes to the "Eukaryotic translation initiation

factor 4A, isoform " nucleic acid or its complement under low stringency conditions, and/or

(xvi) "FLJ13910" (SEQ ID No:57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13910", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13910" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "FRAP1" (SEQ ID No:58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FRAP1", the variant being encoded by a nucleic acid that hybridizes to the "FRAP1" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "GTP-binding protein ERA" (SEQ ID No:59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "GTP-binding protein ERA", the variant being encoded by a nucleic acid that hybridizes to the "GTP-binding protein ERA" nucleic acid or its complement under low stringency conditions, and/or

(xix) "HDAC2" (SEQ ID No:60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HDAC2", the variant being encoded by a nucleic acid that hybridizes to the "HDAC2" nucleic acid or its complement under low stringency conditions, and/or

(xx) "HERC2 protein" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HERC2 protein", the variant being encoded by a nucleic acid that hybridizes to the "HERC2 protein" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "HSPC154" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC154", the variant being encoded by a nucleic acid that hybridizes to the "HSPC154" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "HSPC245" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC245", the variant being encoded by a nucleic acid that hybridizes to the "HSPC245" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "IKAP" (SEQ ID No:64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "IKAP", the variant being

encoded by a nucleic acid that hybridizes to the "IKAP" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "Insulinoma-glucagonoma protein 20" (SEQ ID No:65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Insulinoma-glucagonoma protein 20", the variant being encoded by a nucleic acid that hybridizes to the "Insulinoma-glucagonoma protein 20" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "KIAA0056" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0056", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0056" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "KIAA0166" (SEQ ID No:67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0166", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0166" nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "KIAA0325" (SEQ ID No:68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0325", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0325" nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "KIAA0564" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0564", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0564" nucleic acid or its complement under low stringency conditions, and/or

(xxix) "KIAA0763" (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0763", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0763" nucleic acid or its complement under low stringency conditions, and/or

(xxx) "LIB ( leucine-rich repeat protein)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "LIB ( leucine-rich repeat protein)", the variant being encoded by a nucleic acid that hybridizes to the "LIB ( leucine-rich repeat protein)" nucleic acid or its complement under low stringency conditions, and/or

(xxxi) "Laminin, gamma 1 " (SEQ ID No:72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Laminin,

gamma 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions, and/or (xxxii) "MBIP" (SEQ ID No:73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MBIP", the variant being encoded by a nucleic acid that hybridizes to the "MBIP" nucleic acid or its complement under low stringency conditions, and/or

(xxxiii) "MEGF7" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEGF7", the variant being encoded by a nucleic acid that hybridizes to the "MEGF7" nucleic acid or its complement under low stringency conditions, and/or

(xxxiv) "Munc18-1" (SEQ ID No:75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Munc18-1", the variant being encoded by a nucleic acid that hybridizes to the "Munc18-1" nucleic acid or its complement under low stringency conditions, and/or

(xxxv) "Myosin IXB" (SEQ ID No:76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Myosin IXB", the variant being encoded by a nucleic acid that hybridizes to the "Myosin IXB" nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "NIPSNAP1" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NIPSNAP1", the variant being encoded by a nucleic acid that hybridizes to the "NIPSNAP1" nucleic acid or its complement under low stringency conditions, and/or

(xxxvii) "NIPSNAP2" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NIPSNAP2", the variant being encoded by a nucleic acid that hybridizes to the "NIPSNAP2" nucleic acid or its complement under low stringency conditions, and/or

(xxxviii) "Neurexin-1" (SEQ ID No:79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurexin-1", the variant being encoded by a nucleic acid that hybridizes to the "Neurexin-1" nucleic acid or its complement under low stringency conditions, and/or

(xxxix) "PDZ and LIM domain protein 1" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PDZ and LIM domain protein 1", the variant being encoded by a nucleic acid

that hybridizes to the "PDZ and LIM domain protein 1" nucleic acid or its complement under low stringency conditions, and/or

(xi) "PILT" (SEQ ID No:81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PILT", the variant being encoded by a nucleic acid that hybridizes to the "PILT" nucleic acid or its complement under low stringency conditions, and/or

(xii) "Paladin" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Paladin", the variant being encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "Peroxisome oxidoreductase 4" (SEQ ID No:83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Peroxisome oxidoreductase 4", the variant being encoded by a nucleic acid that hybridizes to the "Peroxisome oxidoreductase 4" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)" (SEQ ID No:84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)", the variant being encoded by a nucleic acid that hybridizes to the "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)" nucleic acid or its complement under low stringency conditions, and/or

(xv) "Procollagen C-endopeptidase enhancer" (SEQ ID No:85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Procollagen C-endopeptidase enhancer", the variant being encoded by a nucleic acid that hybridizes to the "Procollagen C-endopeptidase enhancer" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "Programmed cell death 10" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Programmed cell death 10", the variant being encoded by a nucleic acid that hybridizes to the "Programmed cell death 10" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "Protein similar to AGCP6688" (SEQ ID No:87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to AGCP6688", the variant being encoded by a nucleic acid that

hybridizes to the "Protein similar to AGCP6688 " nucleic acid or its complement under low stringency conditions, and/or

(xlvii) "RPGR-interacting protein 1" (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RPGR-interacting protein 1", the variant being encoded by a nucleic acid that hybridizes to the "RPGR-interacting protein 1" nucleic acid or its complement under low stringency conditions, and/or

(xlviii) "Reelin" (SEQ ID No:89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Reelin", the variant being encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, and/or

(xlix) "Serine/threonine protein phosphatase 6 " (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Serine/threonine protein phosphatase 6 ", the variant being encoded by a nucleic acid that hybridizes to the "Serine/threonine protein phosphatase 6 " nucleic acid or its complement under low stringency conditions, and/or

(l) "Sortilin-related receptor " (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin-related receptor ", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin-related receptor " nucleic acid or its complement under low stringency conditions, and/or

(li) "Synaptogyrin 3" (SEQ ID No:92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Synaptogyrin 3", the variant being encoded by a nucleic acid that hybridizes to the "Synaptogyrin 3" nucleic acid or its complement under low stringency conditions, and/or

(lii) "Syntaxin-1" (SEQ ID No:93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Syntaxin-1", the variant being encoded by a nucleic acid that hybridizes to the "Syntaxin-1" nucleic acid or its complement under low stringency conditions, and/or

(liii) "Ubiquitin-protein ligase E3-alpha " (SEQ ID No:94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquitin-protein ligase E3-alpha ", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquitin-protein ligase E3-alpha " nucleic acid or its complement under low stringency conditions, and/or

(liv) "VGF nerve growth factor inducible protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "VGF nerve growth factor inducible protein", the variant being encoded by a nucleic acid that hybridizes to the "VGF nerve growth factor inducible protein" nucleic acid or its complement under low stringency conditions, and/or

(lv) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and/or

(lvi) "Zinc finger protein 198 " (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Zinc finger protein 198 ", the variant being encoded by a nucleic acid that hybridizes to the "Zinc finger protein 198 " nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; inflammatory conditions such as ulcerative colitis, Crohn's disease and arteriosclerosis.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; inflammatory conditions such as ulcerative colitis, Crohn's disease and arteriosclerosis.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition

of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether  
 (i) "ADAMTS-19" (SEQ ID No:44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADAMTS-19", the variant being encoded by a nucleic acid that hybridizes to the "ADAMTS-19" nucleic acid or its complement under low stringency conditions, and/or  
 (ii) "APLP1" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP1", the variant being encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or

- (iii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Axonemal dynein heavy chain 8" (SEQ ID No:45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Axonemal dynein heavy chain 8", the variant being encoded by a nucleic acid that hybridizes to the "Axonemal dynein heavy chain 8" nucleic acid or its complement under low stringency conditions, and/or
- (v) "Cadherin EGF LAG seven-pass G-type receptor 2 " (SEQ ID No:46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2 " nucleic acid or its complement under low stringency conditions, and/or
- (vi) "Calsyntenin-1" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-1", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-1" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "Calsyntenin-2" (SEQ ID No:48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-2", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-2" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "Calsyntenin-3" (SEQ ID No:49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-3", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-3" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Chondroitin sulfate proteoglycan 6 " (SEQ ID No:50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Chondroitin sulfate proteoglycan 6 ", the variant being encoded by a nucleic acid that hybridizes to the "Chondroitin sulfate proteoglycan 6 " nucleic acid or its complement under low stringency conditions, and/or
- (x) "Chromatin-specific transcription elongation factor FACT 140 kDa subunit" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment

thereof, or a homologue thereof, or a variant of "Chromatin-specific transcription elongation factor FACT 140 kDa subunit", the variant being encoded by a nucleic acid that hybridizes to the "Chromatin-specific transcription elongation factor FACT 140 kDa subunit" nucleic acid or its complement under low stringency conditions, and/or

(xi) "DC6 protein" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DC6 protein", the variant being encoded by a nucleic acid that hybridizes to the "DC6 protein" nucleic acid or its complement under low stringency conditions, and/or

(xii) "Dynein light chain 2A " (SEQ ID No:53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynein light chain 2A ", the variant being encoded by a nucleic acid that hybridizes to the "Dynein light chain 2A " nucleic acid or its complement under low stringency conditions, and/or

(xiii) "Dynein light chain-A " (SEQ ID No:54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynein light chain-A ", the variant being encoded by a nucleic acid that hybridizes to the "Dynein light chain-A " nucleic acid or its complement under low stringency conditions, and/or

(xiv) "ENG00000168820 (hypothetical protein with p-loop)" (SEQ ID No:55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENG00000168820 (hypothetical protein with p-loop)", the variant being encoded by a nucleic acid that hybridizes to the "ENG00000168820 (hypothetical protein with p-loop)" nucleic acid or its complement under low stringency conditions, and/or

(xv) "Eukaryotic translation initiation factor 4A, isoform " (SEQ ID No:56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Eukaryotic translation initiation factor 4A, isoform ", the variant being encoded by a nucleic acid that hybridizes to the "Eukaryotic translation initiation factor 4A, isoform " nucleic acid or its complement under low stringency conditions, and/or

(xvi) "FLJ13910" (SEQ ID No:57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13910", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13910" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "FRAP1" (SEQ ID No:58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FRAP1", the variant being encoded by a nucleic acid that hybridizes to the "FRAP1" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "GTP-binding protein ERA" (SEQ ID No:59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "GTP-binding protein ERA", the variant being encoded by a nucleic acid that hybridizes to the "GTP-binding protein ERA" nucleic acid or its complement under low stringency conditions, and/or

(xix) "HDAC2" (SEQ ID No:60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HDAC2", the variant being encoded by a nucleic acid that hybridizes to the "HDAC2" nucleic acid or its complement under low stringency conditions, and/or

(xx) "HERC2 protein" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HERC2 protein", the variant being encoded by a nucleic acid that hybridizes to the "HERC2 protein" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "HSPC154" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC154", the variant being encoded by a nucleic acid that hybridizes to the "HSPC154" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "HSPC245" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC245", the variant being encoded by a nucleic acid that hybridizes to the "HSPC245" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "IKAP" (SEQ ID No:64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "IKAP", the variant being encoded by a nucleic acid that hybridizes to the "IKAP" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "Insulinoma-glucagonoma protein 20" (SEQ ID No:65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Insulinoma-glucagonoma protein 20", the variant being encoded by a nucleic acid that hybridizes to the "Insulinoma-glucagonoma protein 20" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "KIAA0056" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0056", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0056" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "KIAA0166" (SEQ ID No:67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0166", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0166" nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "KIAA0325" (SEQ ID No:68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0325", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0325" nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "KIAA0564" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0564", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0564" nucleic acid or its complement under low stringency conditions, and/or

(xxix) "KIAA0763" (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0763", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0763" nucleic acid or its complement under low stringency conditions, and/or

(xxx) "LIB ( leucine-rich repeat protein)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "LIB ( leucine-rich repeat protein)", the variant being encoded by a nucleic acid that hybridizes to the "LIB ( leucine-rich repeat protein)" nucleic acid or its complement under low stringency conditions, and/or

(xxxi) "Laminin, gamma 1 " (SEQ ID No:72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Laminin, gamma 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions, and/or

(xxxii) "MBIP" (SEQ ID No:73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MBIP", the variant being encoded by a nucleic acid that hybridizes to the "MBIP" nucleic acid or its complement under low stringency conditions, and/or

- (xxxiii) "MEGF7" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEGF7", the variant being encoded by a nucleic acid that hybridizes to the "MEGF7" nucleic acid or its complement under low stringency conditions, and/or
- (xxxiv) "Munc18-1" (SEQ ID No:75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Munc18-1", the variant being encoded by a nucleic acid that hybridizes to the "Munc18-1" nucleic acid or its complement under low stringency conditions, and/or
- (xxxv) "Myosin IXB" (SEQ ID No:76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Myosin IXB", the variant being encoded by a nucleic acid that hybridizes to the "Myosin IXB" nucleic acid or its complement under low stringency conditions, and/or
- (xxxvi) "NIPSNAP1" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NIPSNAP1", the variant being encoded by a nucleic acid that hybridizes to the "NIPSNAP1" nucleic acid or its complement under low stringency conditions, and/or
- (xxxvii) "NIPSNAP2" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NIPSNAP2", the variant being encoded by a nucleic acid that hybridizes to the "NIPSNAP2" nucleic acid or its complement under low stringency conditions, and/or
- (xxxviii) "Neurexin-1" (SEQ ID No:79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurexin-1", the variant being encoded by a nucleic acid that hybridizes to the "Neurexin-1" nucleic acid or its complement under low stringency conditions, and/or
- (xxxix) "PDZ and LIM domain protein 1" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PDZ and LIM domain protein 1", the variant being encoded by a nucleic acid that hybridizes to the "PDZ and LIM domain protein 1" nucleic acid or its complement under low stringency conditions, and/or
- (xl) "PILT" (SEQ ID No:81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PILT", the variant being encoded by a nucleic acid that hybridizes to the "PILT" nucleic acid or its complement under low stringency conditions, and/or

(xli) "Paladin" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Paladin", the variant being encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or

(xlii) "Peroxiredoxin 4" (SEQ ID No:83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Peroxiredoxin 4", the variant being encoded by a nucleic acid that hybridizes to the "Peroxiredoxin 4" nucleic acid or its complement under low stringency conditions, and/or

(xliii) "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)" (SEQ ID No:84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)", the variant being encoded by a nucleic acid that hybridizes to the "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)" nucleic acid or its complement under low stringency conditions, and/or

(xliv) "Procollagen C-endopeptidase enhancer " (SEQ ID No:85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Procollagen C-endopeptidase enhancer ", the variant being encoded by a nucleic acid that hybridizes to the "Procollagen C-endopeptidase enhancer " nucleic acid or its complement under low stringency conditions, and/or

(xlv) "Programmed cell death 10" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Programmed cell death 10", the variant being encoded by a nucleic acid that hybridizes to the "Programmed cell death 10" nucleic acid or its complement under low stringency conditions, and/or

(xlvi) "Protein similar to AGCP6688 " (SEQ ID No:87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to AGCP6688 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to AGCP6688 " nucleic acid or its complement under low stringency conditions, and/or

(xlvii) "RPGR-interacting protein 1" (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RPGR-interacting protein 1", the variant being encoded by a nucleic acid that hybridizes to the "RPGR-interacting protein 1" nucleic acid or its complement under low stringency conditions, and/or

(xlviii) "Reelin" (SEQ ID No:89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Reelin", the variant being encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, and/or

(xlix) "Serine/threonine protein phosphatase 6 " (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Serine/threonine protein phosphatase 6 ", the variant being encoded by a nucleic acid that hybridizes to the "Serine/threonine protein phosphatase 6 " nucleic acid or its complement under low stringency conditions, and/or

(l) "Sortilin-related receptor " (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin-related receptor ", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin-related receptor " nucleic acid or its complement under low stringency conditions, and/or

(li) "Synaptogyrin 3" (SEQ ID No:92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Synaptogyrin 3", the variant being encoded by a nucleic acid that hybridizes to the "Synaptogyrin 3" nucleic acid or its complement under low stringency conditions, and/or

(lii) "Syntaxin-1" (SEQ ID No:93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Syntaxin-1", the variant being encoded by a nucleic acid that hybridizes to the "Syntaxin-1" nucleic acid or its complement under low stringency conditions, and/or

(liii) "Ubiquitin-protein ligase E3-alpha " (SEQ ID No:94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquitin-protein ligase E3-alpha ", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquitin-protein ligase E3-alpha " nucleic acid or its complement under low stringency conditions, and/or

(liv) "VGF nerve growth factor inducible protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "VGF nerve growth factor inducible protein", the variant being encoded by a nucleic acid that hybridizes to the "VGF nerve growth factor inducible protein" nucleic acid or its complement under low stringency conditions, and/or

(lv) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant

being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and/or

(Ivi) "Zinc finger protein 198 " (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Zinc finger protein 198 ", the variant being encoded by a nucleic acid that hybridizes to the "Zinc finger protein 198 " nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease; inflammatory conditions such as ulcerative colitis, Crohn's disease and arteriosclerosis.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the regulation of APP processing and APP function of, or protein composition of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins:

(i) "ADAMTS-19" (SEQ ID No:44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADAMTS-19", the variant being encoded by a nucleic acid that hybridizes to the "ADAMTS-19" nucleic acid or its complement under low stringency conditions,

(ii) "APLP1" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APLP1", the variant

being encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "Axonemal dynein heavy chain 8" (SEQ ID No:45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Axonemal dynein heavy chain 8", the variant being encoded by a nucleic acid that hybridizes to the "Axonemal dynein heavy chain 8" nucleic acid or its complement under low stringency conditions,

(v) "Cadherin EGF LAG seven-pass G-type receptor 2 " (SEQ ID No:46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2 " nucleic acid or its complement under low stringency conditions,

(vi) "Calsyntenin-1" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-1", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-1" nucleic acid or its complement under low stringency conditions,

(vii) "Calsyntenin-2" (SEQ ID No:48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-2", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-2" nucleic acid or its complement under low stringency conditions,

(viii) "Calsyntenin-3" (SEQ ID No:49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin-3", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin-3" nucleic acid or its complement under low stringency conditions,

(ix) "Chondroitin sulfate proteoglycan 6 " (SEQ ID No:50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Chondroitin sulfate proteoglycan 6 ", the variant being encoded by a nucleic acid that hybridizes to the "Chondroitin sulfate proteoglycan 6 " nucleic acid or its complement under low stringency conditions,

- (x) "Chromatin-specific transcription elongation factor FACT 140 kDa subunit" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Chromatin-specific transcription elongation factor FACT 140 kDa subunit", the variant being encoded by a nucleic acid that hybridizes to the "Chromatin-specific transcription elongation factor FACT 140 kDa subunit" nucleic acid or its complement under low stringency conditions,
- (xi) "DC6 protein" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DC6 protein", the variant being encoded by a nucleic acid that hybridizes to the "DC6 protein" nucleic acid or its complement under low stringency conditions,
- (xii) "Dynein light chain 2A " (SEQ ID No:53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynein light chain 2A ", the variant being encoded by a nucleic acid that hybridizes to the "Dynein light chain 2A " nucleic acid or its complement under low stringency conditions,
- (xiii) "Dynein light chain-A " (SEQ ID No:54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynein light chain-A ", the variant being encoded by a nucleic acid that hybridizes to the "Dynein light chain-A " nucleic acid or its complement under low stringency conditions,
- (xiv) "ENG00000168820 (hypothetical protein with p-loop)" (SEQ ID No:55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENG00000168820 (hypothetical protein with p-loop)", the variant being encoded by a nucleic acid that hybridizes to the "ENG00000168820 (hypothetical protein with p-loop)" nucleic acid or its complement under low stringency conditions,
- (xv) "Eukaryotic translation initiation factor 4A, isoform " (SEQ ID No:56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Eukaryotic translation initiation factor 4A, isoform ", the variant being encoded by a nucleic acid that hybridizes to the "Eukaryotic translation initiation factor 4A, isoform " nucleic acid or its complement under low stringency conditions,
- (xvi) "FLJ13910" (SEQ ID No:57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13910", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13910" nucleic acid or its complement under low stringency conditions,

(xvii) "FRAP1" (SEQ ID No:58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FRAP1", the variant being encoded by a nucleic acid that hybridizes to the "FRAP1" nucleic acid or its complement under low stringency conditions,

(xviii) "GTP-binding protein ERA" (SEQ ID No:59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "GTP-binding protein ERA", the variant being encoded by a nucleic acid that hybridizes to the "GTP-binding protein ERA" nucleic acid or its complement under low stringency conditions,

(xix) "HDAC2" (SEQ ID No:60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HDAC2", the variant being encoded by a nucleic acid that hybridizes to the "HDAC2" nucleic acid or its complement under low stringency conditions,

(xx) "HERC2 protein" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HERC2 protein", the variant being encoded by a nucleic acid that hybridizes to the "HERC2 protein" nucleic acid or its complement under low stringency conditions,

(xxi) "HSPC154" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC154", the variant being encoded by a nucleic acid that hybridizes to the "HSPC154" nucleic acid or its complement under low stringency conditions,

(xxii) "HSPC245" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HSPC245", the variant being encoded by a nucleic acid that hybridizes to the "HSPC245" nucleic acid or its complement under low stringency conditions,

(xxiii) "IKAP" (SEQ ID No:64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "IKAP", the variant being encoded by a nucleic acid that hybridizes to the "IKAP" nucleic acid or its complement under low stringency conditions,

(xxiv) "Insulinoma-glucagonoma protein 20" (SEQ ID No:65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Insulinoma-glucagonoma protein 20", the variant being encoded by a nucleic acid that hybridizes to the "Insulinoma-glucagonoma protein 20" nucleic acid or its complement under low stringency conditions,

(xxv) "KIAA0056" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0056", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0056" nucleic acid or its complement under low stringency conditions,

(xxvi) "KIAA0166" (SEQ ID No:67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0166", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0166" nucleic acid or its complement under low stringency conditions,

(xxvii) "KIAA0325" (SEQ ID No:68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0325", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0325" nucleic acid or its complement under low stringency conditions,

(xxviii) "KIAA0564" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0564", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0564" nucleic acid or its complement under low stringency conditions,

(xxix) "KIAA0763" (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0763", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0763" nucleic acid or its complement under low stringency conditions,

(xxx) "LIB ( leucine-rich repeat protein)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "LIB ( leucine-rich repeat protein)", the variant being encoded by a nucleic acid that hybridizes to the "LIB ( leucine-rich repeat protein)" nucleic acid or its complement under low stringency conditions,

(xxxi) "Laminin, gamma 1 " (SEQ ID No:72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Laminin, gamma 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1-" nucleic acid or its complement under low stringency conditions,

(xxxii) "MBIP" (SEQ ID No:73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MBIP", the variant being encoded by a nucleic acid that hybridizes to the "MBIP" nucleic acid or its complement under low stringency conditions,

- (xxxiii) "MEGF7" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEGF7", the variant being encoded by a nucleic acid that hybridizes to the "MEGF7" nucleic acid or its complement under low stringency conditions,
- (xxxiv) "Munc18-1" (SEQ ID No:75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Munc18-1", the variant being encoded by a nucleic acid that hybridizes to the "Munc18-1" nucleic acid or its complement under low stringency conditions,
- (xxxv) "Myosin IXB" (SEQ ID No:76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Myosin IXB", the variant being encoded by a nucleic acid that hybridizes to the "Myosin IXB" nucleic acid or its complement under low stringency conditions,
- (xxxvi) "NIPSNAP1" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NIPSNAP1", the variant being encoded by a nucleic acid that hybridizes to the "NIPSNAP1" nucleic acid or its complement under low stringency conditions,
- (xxxvii) "NIPSNAP2" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NIPSNAP2", the variant being encoded by a nucleic acid that hybridizes to the "NIPSNAP2" nucleic acid or its complement under low stringency conditions,
- (xxxviii) "Neurexin-1" (SEQ ID No:79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurexin-1", the variant being encoded by a nucleic acid that hybridizes to the "Neurexin-1" nucleic acid or its complement under low stringency conditions,
- (xxxix) "PDZ and LIM domain protein 1" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PDZ and LIM domain protein 1", the variant being encoded by a nucleic acid that hybridizes to the "PDZ and LIM domain protein 1" nucleic acid or its complement under low stringency conditions,
- (xl) "PILT" (SEQ ID No:81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PILT", the variant being encoded by a nucleic acid that hybridizes to the "PILT" nucleic acid or its complement under low stringency conditions,

(xli) "Paladin" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Paladin", the variant being encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xlii) "Peroxiredoxin 4" (SEQ ID No:83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Peroxiredoxin 4", the variant being encoded by a nucleic acid that hybridizes to the "Peroxiredoxin 4" nucleic acid or its complement under low stringency conditions,

(xliii) "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)" (SEQ ID No:84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)", the variant being encoded by a nucleic acid that hybridizes to the "Phosphoenolpyruvate carboxykinase 2 (mitochondrial)" nucleic acid or its complement under low stringency conditions,

(xliv) "Procollagen C-endopeptidase enhancer " (SEQ ID No:85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Procollagen C-endopeptidase enhancer ", the variant being encoded by a nucleic acid that hybridizes to the "Procollagen C-endopeptidase enhancer " nucleic acid or its complement under low stringency conditions,

(xlv) "Programmed cell death 10" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Programmed cell death 10", the variant being encoded by a nucleic acid that hybridizes to the "Programmed cell death 10" nucleic acid or its complement under low stringency conditions,

(xlvi) "Protein similar to AGCP6688 " (SEQ ID No:87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to AGCP6688 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to AGCP6688 " nucleic acid or its complement under low stringency conditions,

(xlvii) "RPGR-interacting protein 1" (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RPGR-interacting protein 1", the variant being encoded by a nucleic acid that hybridizes to the "RPGR-interacting protein 1" nucleic acid or its complement under low stringency conditions,

(xlviii) "Reelin" (SEQ ID No:89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Reelin", the variant being encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,

(xlix) "Serine/threonine protein phosphatase 6 " (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Serine/threonine protein phosphatase 6 ", the variant being encoded by a nucleic acid that hybridizes to the "Serine/threonine protein phosphatase 6 " nucleic acid or its complement under low stringency conditions,

(l) "Sortilin-related receptor " (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin-related receptor ", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin-related receptor " nucleic acid or its complement under low stringency conditions,

(li) "Synaptogyrin 3" (SEQ ID No:92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Synaptogyrin 3", the variant being encoded by a nucleic acid that hybridizes to the "Synaptogyrin 3" nucleic acid or its complement under low stringency conditions,

(lii) "Syntaxin-1" (SEQ ID No:93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Syntaxin-1", the variant being encoded by a nucleic acid that hybridizes to the "Syntaxin-1" nucleic acid or its complement under low stringency conditions,

(liii) "Ubiquitin-protein ligase E3-alpha " (SEQ ID No:94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquitin-protein ligase E3-alpha ", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquitin-protein ligase E3-alpha " nucleic acid or its complement under low stringency conditions,

(liv) "VGF nerve growth factor inducible protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "VGF nerve growth factor inducible protein", the variant being encoded by a nucleic acid that hybridizes to the "VGF nerve growth factor inducible protein" nucleic acid or its complement under low stringency conditions,

(lv) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant

being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and/or (Ivi) "Zinc finger protein 198 " (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Zinc finger protein 198 ", the variant being encoded by a nucleic acid that hybridizes to the "Zinc finger protein 198 " nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease; inflammatory conditions such as ulcerative colitis, Crohn's disease and atherosclerosis.

The invention further relates to the Presenilin 2 complex:

1. A protein complex selected from complex (I) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "DOCK3" (SEQ ID No:111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DOCK3", the variant being encoded by a nucleic acid that hybridizes to the "DOCK3" nucleic acid or its complement under low stringency conditions,

(ii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and

(iii) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

(i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(ii) "200 kDa proteasome activator " (SEQ ID No:99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "200 kDa proteasome activator ", the variant being encoded by a nucleic acid that hybridizes to the "200 kDa proteasome activator " nucleic acid or its complement under low stringency conditions,

(iii) "ADP-ribosylation factor 3" (SEQ ID No:100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADP-ribosylation factor 3", the variant being encoded by a nucleic acid that hybridizes to the "ADP-ribosylation factor 3" nucleic acid or its complement under low stringency conditions,

(iv) "ATP-binding cassette protein, sub-family B, member 1" (SEQ ID No:101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette protein, sub-family B, member 1", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette protein, sub-family B, member 1" nucleic acid or its complement under low stringency conditions,

(v) "ATP-dependent metalloprotease FtsH1 homologue " (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-dependent metalloprotease FtsH1 homologue.", the variant being encoded by a nucleic acid that hybridizes to the "ATP-dependent metalloprotease FtsH1 homologue " nucleic acid or its complement under low stringency conditions,

(vi) "Acetolactate synthase " (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Acetolactate synthase ", the variant being encoded by a nucleic acid that hybridizes to the "Acetolactate synthase " nucleic acid or its complement under low stringency conditions,

(vii) "Adrenoleukodystrophy protein" (SEQ ID No:104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Adrenoleukodystrophy protein", the variant being encoded by a nucleic acid that hybridizes to the "Adrenoleukodystrophy protein" nucleic acid or its complement under low stringency conditions,

(viii) "CGI-51" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-51", the

variant being encoded by a nucleic acid that hybridizes to the "CGI-51" nucleic acid or its complement under low stringency conditions,

(ix) "Calcium-binding protein P22" (SEQ ID No:106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calcium-binding protein P22", the variant being encoded by a nucleic acid that hybridizes to the "Calcium-binding protein P22" nucleic acid or its complement under low stringency conditions,

(x) "Cation-chloride cotransporter-interacting protein " (SEQ ID No:107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cation-chloride cotransporter-interacting protein ", the variant being encoded by a nucleic acid that hybridizes to the "Cation-chloride cotransporter-interacting protein " nucleic acid or its complement under low stringency conditions,

(xi) "Centromere/kinetochore protein ZW10 homologue " (SEQ ID No:108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Centromere/kinetochore protein ZW10 homologue ", the variant being encoded by a nucleic acid that hybridizes to the "Centromere/kinetochore protein ZW10 homologue " nucleic acid or its complement under low stringency conditions,

(xii) "Cerebral protein 10" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein 10", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein 10" nucleic acid or its complement under low stringency conditions,

(xiii) "DKFZp586c1924 " (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DKFZp586c1924 ", the variant being encoded by a nucleic acid that hybridizes to the "DKFZp586c1924 " nucleic acid or its complement under low stringency conditions,

(xiv) "Down syndrome critical region protein 2" (SEQ ID No:112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Down syndrome critical region protein 2", the variant being encoded by a nucleic acid that hybridizes to the "Down syndrome critical region protein 2" nucleic acid or its complement under low stringency conditions,

(xv) "ECSIT" (SEQ ID No:113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ECSIT", the variant

being encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(xvi) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions,

(xvii) "FLJ20420" (SEQ ID No:115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20420", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20420" nucleic acid or its complement under low stringency conditions,

(xviii) "FLJ22555" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22555", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22555" nucleic acid or its complement under low stringency conditions,

(xix) "FLJ22678" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22678", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22678" nucleic acid or its complement under low stringency conditions,

(xx) "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" (SEQ ID No:118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3", the variant being encoded by a nucleic acid that hybridizes to the "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" nucleic acid or its complement under low stringency conditions,

(xxi) "HTRA2" (SEQ ID No:119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HTRA2", the variant being encoded by a nucleic acid that hybridizes to the "HTRA2" nucleic acid or its complement under low stringency conditions,

(xxii) "HU-K4 " (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4 ", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4 " nucleic acid or its complement under low stringency conditions,

(xxiii) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062",

the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions,

(xxiv) "KIAA0090" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0090", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,

(xxv) "KIAA0103" (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0103", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0103" nucleic acid or its complement under low stringency conditions,

(xxvi) "KIAA1499" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1499", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1499" nucleic acid or its complement under low stringency conditions,

(xxvii) "MGC4248 " (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248 ", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248 " nucleic acid or its complement under low stringency conditions,

(xxviii) "NICE-3" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NICE-3", the variant being encoded by a nucleic acid that hybridizes to the "NICE-3" nucleic acid or its complement under low stringency conditions,

(xxix) "NPD002 " (SEQ ID No:127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NPD002 ", the variant being encoded by a nucleic acid that hybridizes to the "NPD002 " nucleic acid or its complement under low stringency conditions,

(xxx) "P63 protein" (SEQ ID No:128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "P63 protein", the variant being encoded by a nucleic acid that hybridizes to the "P63 protein" nucleic acid or its complement under low stringency conditions,

(xxxi) "PSMA1 " (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA1 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMA1 " nucleic acid or its complement under low stringency conditions,

- (xxxii) "PSMA3 " (SEQ ID No:130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA3 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMA3 " nucleic acid or its complement under low stringency conditions,
- (xxxiii) "PSMA4" (SEQ ID No:131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA4", the variant being encoded by a nucleic acid that hybridizes to the "PSMA4" nucleic acid or its complement under low stringency conditions,
- (xxxiv) "PSMA6" (SEQ ID No:132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA6", the variant being encoded by a nucleic acid that hybridizes to the "PSMA6" nucleic acid or its complement under low stringency conditions,
- (xxxv) "PSMB1" (SEQ ID No:133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB1", the variant being encoded by a nucleic acid that hybridizes to the "PSMB1" nucleic acid or its complement under low stringency conditions,
- (xxxvi) "PSMB2" (SEQ ID No:134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB2", the variant being encoded by a nucleic acid that hybridizes to the "PSMB2" nucleic acid or its complement under low stringency conditions,
- (xxxvii) "PSMB3" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB3", the variant being encoded by a nucleic acid that hybridizes to the "PSMB3" nucleic acid or its complement under low stringency conditions,
- (xxxviii) "PSMB4 " (SEQ ID No:136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB4 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMB4 " nucleic acid or its complement under low stringency conditions,
- (xxxix) "PSMB5" (SEQ ID No:137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB5", the variant being encoded by a nucleic acid that hybridizes to the "PSMB5" nucleic acid or its complement under low stringency conditions,
- (xl) "PSMB6" (SEQ ID No:138) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB6", the variant

being encoded by a nucleic acid that hybridizes to the "PSMB6" nucleic acid or its complement under low stringency conditions,

(xli) "PSMC1" (SEQ ID No:139) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC1", the variant being encoded by a nucleic acid that hybridizes to the "PSMC1" nucleic acid or its complement under low stringency conditions,

(xlii) "PSMC2" (SEQ ID No:140) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC2", the variant being encoded by a nucleic acid that hybridizes to the "PSMC2" nucleic acid or its complement under low stringency conditions,

(xliii) "PSMC3" (SEQ ID No:141) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC3", the variant being encoded by a nucleic acid that hybridizes to the "PSMC3" nucleic acid or its complement under low stringency conditions,

(xliv) "PSMC4" (SEQ ID No:142) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC4", the variant being encoded by a nucleic acid that hybridizes to the "PSMC4" nucleic acid or its complement under low stringency conditions,

(xlv) "PSMC5" (SEQ ID No:143) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC5", the variant being encoded by a nucleic acid that hybridizes to the "PSMC5" nucleic acid or its complement under low stringency conditions,

(xlvi) "PSMC6" (SEQ ID No:144) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC6", the variant being encoded by a nucleic acid that hybridizes to the "PSMC6" nucleic acid or its complement under low stringency conditions,

(xlvii) "PSMD1" (SEQ ID No:145) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD1", the variant being encoded by a nucleic acid that hybridizes to the "PSMD1" nucleic acid or its complement under low stringency conditions,

(xlviii) "PSMD11" (SEQ ID No:146) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD11", the variant being encoded by a nucleic acid that hybridizes to the "PSMD11" nucleic acid or its complement under low stringency conditions,

(xlix) "PSMD12" (SEQ ID No:147) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD12", the variant being encoded by a nucleic acid that hybridizes to the "PSMD12" nucleic acid or its complement under low stringency conditions,

(l) "PSMD13" (SEQ ID No:148) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD13", the variant being encoded by a nucleic acid that hybridizes to the "PSMD13" nucleic acid or its complement under low stringency conditions,

(li) "PSMD2" (SEQ ID No:149) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD2", the variant being encoded by a nucleic acid that hybridizes to the "PSMD2" nucleic acid or its complement under low stringency conditions,

(lii) "PSMD3" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD3", the variant being encoded by a nucleic acid that hybridizes to the "PSMD3" nucleic acid or its complement under low stringency conditions,

(liii) "PSMD4" (SEQ ID No:151) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD4", the variant being encoded by a nucleic acid that hybridizes to the "PSMD4" nucleic acid or its complement under low stringency conditions,

(liv) "Prohibitin" (SEQ ID No:153) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Prohibitin", the variant being encoded by a nucleic acid that hybridizes to the "Prohibitin" nucleic acid or its complement under low stringency conditions,

(lv) "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 " (SEQ ID No:154) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 " nucleic acid or its complement under low stringency conditions,

(lvi) "Serine/threonine protein phosphatase 6" (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Serine/threonine protein phosphatase 6", the variant being encoded by a

nucleic acid that hybridizes to the "Serine/threonine protein phosphatase 6" nucleic acid or its complement under low stringency conditions,

(lvii) "Sortilin 1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin 1" nucleic acid or its complement under low stringency conditions,

(lviii) "Stearoyl-CoA desaturase " (SEQ ID No:155) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stearoyl-CoA desaturase ", the variant being encoded by a nucleic acid that hybridizes to the "Stearoyl-CoA desaturase " nucleic acid or its complement under low stringency conditions,

(lix) "Ubiquitin-protein ligase EDD " (SEQ ID No:156) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquitin-protein ligase EDD ", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquitin-protein ligase EDD " nucleic acid or its complement under low stringency conditions,

(lx) "Voltage-dependent anion channel 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 2", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 2" nucleic acid or its complement under low stringency conditions, and

(lxi) "Wolframin" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Wolframin", the variant being encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. The protein complex according to No. 1 wherein the first protein is the protein "Presenilin 2" (SEQ ID No:152), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid under low stringency conditions.

3. The protein complex according to No. 1 comprising the following proteins:

(i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(ii) "200 kDa proteasome activator " (SEQ ID No:99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "200 kDa proteasome activator ", the variant being encoded by a nucleic acid that hybridizes to the "200 kDa proteasome activator " nucleic acid or its complement under low stringency conditions,

(iii) "ADP-ribosylation factor 3" (SEQ ID No:100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADP-ribosylation factor 3", the variant being encoded by a nucleic acid that hybridizes to the "ADP-ribosylation factor 3" nucleic acid or its complement under low stringency conditions,

(iv) "ATP-binding cassette protein, sub-family B, member 1" (SEQ ID No:101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette protein, sub-family B, member 1", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette protein, sub-family B, member 1" nucleic acid or its complement under low stringency conditions,

(v) "ATP-dependent metalloprotease FtsH1 homologue " (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-dependent metalloprotease FtsH1 homologue ", the variant being encoded by a nucleic acid that hybridizes to the "ATP-dependent metalloprotease FtsH1 homologue " nucleic acid or its complement under low stringency conditions,

(vi) "Acetolactate synthase " (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Acetolactate synthase ", the variant being encoded by a nucleic acid that hybridizes to the "Acetolactate synthase " nucleic acid or its complement under low stringency conditions,

(vii) "Adrenoleukodystrophy protein" (SEQ ID No:104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Adrenoleukodystrophy protein", the variant being encoded by a nucleic acid that hybridizes to the "Adrenoleukodystrophy protein" nucleic acid or its complement under low stringency conditions,

(viii) "CGI-51" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-51", the variant being encoded by a nucleic acid that hybridizes to the "CGI-51" nucleic acid or its complement under low stringency conditions,

(ix) "Calcium-binding protein P22" (SEQ ID No:106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calcium-binding protein P22", the variant being encoded by a nucleic acid that hybridizes to the "Calcium-binding protein P22" nucleic acid or its complement under low stringency conditions,

(x) "Cation-chloride cotransporter-interacting protein " (SEQ ID No:107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cation-chloride cotransporter-interacting protein ", the variant being encoded by a nucleic acid that hybridizes to the "Cation-chloride cotransporter-interacting protein " nucleic acid or its complement under low stringency conditions,

(xi) "Centromere/kinetochore protein ZW10 homologue " (SEQ ID No:108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Centromere/kinetochore protein ZW10 homologue ", the variant being encoded by a nucleic acid that hybridizes to the "Centromere/kinetochore protein ZW10 homologue " nucleic acid or its complement under low stringency conditions,

(xii) "Cerebral protein 10" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein 10", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein 10" nucleic acid or its complement under low stringency conditions,

- (xiii) "DKFZp586c1924 " (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DKFZp586c1924 ", the variant being encoded by a nucleic acid that hybridizes to the "DKFZp586c1924 " nucleic acid or its complement under low stringency conditions,
- (xiv) "DOCK3" (SEQ ID No:111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DOCK3", the variant being encoded by a nucleic acid that hybridizes to the "DOCK3" nucleic acid or its complement under low stringency conditions,
- (xv) "Down syndrome critical region protein 2" (SEQ ID No:112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Down syndrome critical region protein 2", the variant being encoded by a nucleic acid that hybridizes to the "Down syndrome critical region protein 2" nucleic acid or its complement under low stringency conditions,
- (xvi) "ECSIT" (SEQ ID No:113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ECSIT", the variant being encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (xvii) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions,
- (xviii) "FLJ20420" (SEQ ID No:115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20420", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20420" nucleic acid or its complement under low stringency conditions,
- (xix) "FLJ22555" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22555", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22555" nucleic acid or its complement under low stringency conditions,
- (xx) "FLJ22678" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22678", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22678" nucleic acid or its complement under low stringency conditions,

(xxi) "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" (SEQ ID No:118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3", the variant being encoded by a nucleic acid that hybridizes to the "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" nucleic acid or its complement under low stringency conditions,

(xxii) "HTRA2" (SEQ ID No:119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HTRA2", the variant being encoded by a nucleic acid that hybridizes to the "HTRA2" nucleic acid or its complement under low stringency conditions,

(xxiii) "HU-K4 " (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4 ", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4 " nucleic acid or its complement under low stringency conditions,

(xxiv) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions,

(xxv) "KIAA0090" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0090", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,

(xxvi) "KIAA0103" (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0103", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0103" nucleic acid or its complement under low stringency conditions,

(xxvii) "KIAA1499" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1499", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1499" nucleic acid or its complement under low stringency conditions,

(xxviii) "MGC4248 " (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248 ", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248 " nucleic acid or its complement under low stringency conditions,

(xxix) "NICE-3" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NICE-3", the variant being encoded by a nucleic acid that hybridizes to the "NICE-3" nucleic acid or its complement under low stringency conditions,

(xxx) "NPD002 " (SEQ ID No:127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NPD002 ", the variant being encoded by a nucleic acid that hybridizes to the "NPD002 " nucleic acid or its complement under low stringency conditions,

(xxxi) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(xxxii) "P63 protein" (SEQ ID No:128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "P63 protein", the variant being encoded by a nucleic acid that hybridizes to the "P63 protein" nucleic acid or its complement under low stringency conditions,

(xxxiii) "PSMA1 " (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA1 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMA1 " nucleic acid or its complement under low stringency conditions,

(xxxiv) "PSMA3 " (SEQ ID No:130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA3 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMA3 " nucleic acid or its complement under low stringency conditions,

(xxxv) "PSMA4" (SEQ ID No:131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA4", the variant being encoded by a nucleic acid that hybridizes to the "PSMA4" nucleic acid or its complement under low stringency conditions,

(xxxvi) "PSMA6" (SEQ ID No:132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA6", the variant being encoded by a nucleic acid that hybridizes to the "PSMA6" nucleic acid or its complement under low stringency conditions,

(xxxvii) "PSMB1" (SEQ ID No:133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB1", the

variant being encoded by a nucleic acid that hybridizes to the "PSMB1" nucleic acid or its complement under low stringency conditions,

(xxxviii) "PSMB2" (SEQ ID No:134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB2", the variant being encoded by a nucleic acid that hybridizes to the "PSMB2" nucleic acid or its complement under low stringency conditions,

(xxxix) "PSMB3" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB3", the variant being encoded by a nucleic acid that hybridizes to the "PSMB3" nucleic acid or its complement under low stringency conditions,

(xl) "PSMB4 " (SEQ ID No:136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB4 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMB4 " nucleic acid or its complement under low stringency conditions,

(xli) "PSMB5" (SEQ ID No:137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB5", the variant being encoded by a nucleic acid that hybridizes to the "PSMB5" nucleic acid or its complement under low stringency conditions,

(xlii) "PSMB6" (SEQ ID No:138) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB6", the variant being encoded by a nucleic acid that hybridizes to the "PSMB6" nucleic acid or its complement under low stringency conditions,

(xliii) "PSMC1" (SEQ ID No:139) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC1", the variant being encoded by a nucleic acid that hybridizes to the "PSMC1" nucleic acid or its complement under low stringency conditions,

(xliv) "PSMC2" (SEQ ID No:140) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC2", the variant being encoded by a nucleic acid that hybridizes to the "PSMC2" nucleic acid or its complement under low stringency conditions,

(xlv) "PSMC3" (SEQ ID No:141) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC3", the variant being encoded by a nucleic acid that hybridizes to the "PSMC3" nucleic acid or its complement under low stringency conditions,

(xlii) "PSMC4" (SEQ ID No:142) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC4", the variant being encoded by a nucleic acid that hybridizes to the "PSMC4" nucleic acid or its complement under low stringency conditions,

(xliii) "PSMC5" (SEQ ID No:143) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC5", the variant being encoded by a nucleic acid that hybridizes to the "PSMC5" nucleic acid or its complement under low stringency conditions,

(xliv) "PSMC6" (SEQ ID No:144) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC6", the variant being encoded by a nucleic acid that hybridizes to the "PSMC6" nucleic acid or its complement under low stringency conditions,

(xlv) "PSMD1" (SEQ ID No:145) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD1", the variant being encoded by a nucleic acid that hybridizes to the "PSMD1" nucleic acid or its complement under low stringency conditions,

(i) "PSMD11" (SEQ ID No:146) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD11", the variant being encoded by a nucleic acid that hybridizes to the "PSMD11" nucleic acid or its complement under low stringency conditions,

(ii) "PSMD12" (SEQ ID No:147) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD12", the variant being encoded by a nucleic acid that hybridizes to the "PSMD12" nucleic acid or its complement under low stringency conditions,

(iii) "PSMD13" (SEQ ID No:148) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD13", the variant being encoded by a nucleic acid that hybridizes to the "PSMD13" nucleic acid or its complement under low stringency conditions,

(iiii) "PSMD2" (SEQ ID No:149) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD2", the variant being encoded by a nucleic acid that hybridizes to the "PSMD2" nucleic acid or its complement under low stringency conditions,

(lv) "PSMD3" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD3",

the variant being encoded by a nucleic acid that hybridizes to the "PSMD3" nucleic acid or its complement under low stringency conditions,

(lv) "PSMD4" (SEQ ID No:151) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD4", the variant being encoded by a nucleic acid that hybridizes to the "PSMD4" nucleic acid or its complement under low stringency conditions,

(lvi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions,

(lvii) "Prohibitin" (SEQ ID No:153) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Prohibitin", the variant being encoded by a nucleic acid that hybridizes to the "Prohibitin" nucleic acid or its complement under low stringency conditions,

(lviii) "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 " (SEQ ID No:154) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 " nucleic acid or its complement under low stringency conditions,

(lix) "Serine/threonine protein phosphatase 6" (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Serine/threonine protein phosphatase 6", the variant being encoded by a nucleic acid that hybridizes to the "Serine/threonine protein phosphatase 6" nucleic acid or its complement under low stringency conditions,

(lx) "Sortilin 1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin 1" nucleic acid or its complement under low stringency conditions,

(lxi) "Stearyl-CoA desaturase " (SEQ ID No:155) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stearyl-CoA desaturase ", the variant being encoded by a nucleic acid that hybridizes to the "Stearyl-CoA desaturase " nucleic acid or its complement under low stringency conditions,

(Ixii) "Ubiquitin-protein ligase EDD " (SEQ ID No:156) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquitin-protein ligase EDD ", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquitin-protein ligase EDD " nucleic acid or its complement under low stringency conditions,

(Ixiii) "Voltage-dependent anion channel 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 2", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 2" nucleic acid or its complement under low stringency conditions, and/or

(Ixiv) "Wolframin" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Wolframin", the variant being encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising at least 4 but no more than 63 of the following proteins:

(i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(ii) "200 kDa proteasome activator " (SEQ ID No:99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "200 kDa proteasome activator ", the variant being encoded by a nucleic acid that hybridizes to the "200 kDa proteasome activator " nucleic acid or its complement under low stringency conditions,

(iii) "ADP-ribosylation factor 3" (SEQ ID No:100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADP-ribosylation factor 3", the variant being encoded by a nucleic acid that hybridizes to the "ADP-ribosylation factor 3" nucleic acid or its complement under low stringency conditions,

(iv) "ATP-binding cassette protein, sub-family B, member 1" (SEQ ID No:101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a

homologue thereof, or a variant of "ATP-binding cassette protein, sub-family B, member 1", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette protein, sub-family B, member 1" nucleic acid or its complement under low stringency conditions,

(v) "ATP-dependent metalloprotease FtsH1 homologue " (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-dependent metalloprotease FtsH1 homologue ", the variant being encoded by a nucleic acid that hybridizes to the "ATP-dependent metalloprotease FtsH1 homologue " nucleic acid or its complement under low stringency conditions,

(vi) "Acetolactate synthase " (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Acetolactate synthase ", the variant being encoded by a nucleic acid that hybridizes to the "Acetolactate synthase " nucleic acid or its complement under low stringency conditions,

(vii) "Adrenoleukodystrophy protein" (SEQ ID No:104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Adrenoleukodystrophy protein", the variant being encoded by a nucleic acid that hybridizes to the "Adrenoleukodystrophy protein" nucleic acid or its complement under low stringency conditions,

(viii) "CGI-51" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-51", the variant being encoded by a nucleic acid that hybridizes to the "CGI-51" nucleic acid or its complement under low stringency conditions,

(ix) "Calcium-binding protein P22" (SEQ ID No:106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calcium-binding protein P22", the variant being encoded by a nucleic acid that hybridizes to the "Calcium-binding protein P22" nucleic acid or its complement under low stringency conditions,

(x) "Cation-chloride cotransporter-interacting protein " (SEQ ID No:107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cation-chloride cotransporter-interacting protein ", the variant being encoded by a nucleic acid that hybridizes to the "Cation-chloride cotransporter-interacting protein " nucleic acid or its complement under low stringency conditions,

- (xi) "Centromere/kinetochore protein ZW10 homologue " (SEQ ID No:108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Centromere/kinetochore protein ZW10 homologue ", the variant being encoded by a nucleic acid that hybridizes to the "Centromere/kinetochore protein ZW10 homologue " nucleic acid or its complement under low stringency conditions,
- (xii) "Cerebral protein 10" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein 10", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein 10" nucleic acid or its complement under low stringency conditions,
- (xiii) "DKFZp586c1924 " (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DKFZp586c1924 ", the variant being encoded by a nucleic acid that hybridizes to the "DKFZp586c1924 " nucleic acid or its complement under low stringency conditions,
- (xiv) "DOCK3" (SEQ ID No:111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DOCK3", the variant being encoded by a nucleic acid that hybridizes to the "DOCK3" nucleic acid or its complement under low stringency conditions,
- (xv) "Down syndrome critical region protein 2" (SEQ ID No:112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Down syndrome critical region protein 2", the variant being encoded by a nucleic acid that hybridizes to the "Down syndrome critical region protein 2" nucleic acid or its complement under low stringency conditions,
- (xvi) "ECSIT" (SEQ ID No:113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ECSIT", the variant being encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (xvii) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions,
- (xviii) "FLJ20420" (SEQ ID No:115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20420",

the variant being encoded by a nucleic acid that hybridizes to the "FLJ20420" nucleic acid or its complement under low stringency conditions,

(xix) "FLJ22555" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22555", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22555" nucleic acid or its complement under low stringency conditions,

(xx) "FLJ22678" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22678", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22678" nucleic acid or its complement under low stringency conditions,

(xxi) "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" (SEQ ID No:118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3", the variant being encoded by a nucleic acid that hybridizes to the "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" nucleic acid or its complement under low stringency conditions,

(xxii) "HTRA2" (SEQ ID No:119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HTRA2", the variant being encoded by a nucleic acid that hybridizes to the "HTRA2" nucleic acid or its complement under low stringency conditions,

(xxiii) "HU-K4 " (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4 ", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4 " nucleic acid or its complement under low stringency conditions,

(xxiv) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions,

(xxv) "KIAA0090" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0090", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,

(xxvi) "KIAA0103" (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0103",

the variant being encoded by a nucleic acid that hybridizes to the "KIAA0103" nucleic acid or its complement under low stringency conditions,

(xxvii) "KIAA1499" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1499", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1499" nucleic acid or its complement under low stringency conditions,

(xxviii) "MGC4248 " (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248 ", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248 " nucleic acid or its complement under low stringency conditions,

(xxix) "NICE-3" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NICE-3", the variant being encoded by a nucleic acid that hybridizes to the "NICE-3" nucleic acid or its complement under low stringency conditions,

(xxx) "NPD002 " (SEQ ID No:127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NPD002 ", the variant being encoded by a nucleic acid that hybridizes to the "NPD002 " nucleic acid or its complement under low stringency conditions,

(xxxi) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(xxxii) "P63 protein" (SEQ ID No:128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "P63 protein", the variant being encoded by a nucleic acid that hybridizes to the "P63 protein" nucleic acid or its complement under low stringency conditions,

(xxxiii) "PSMA1 " (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA1 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMA1 " nucleic acid or its complement under low stringency conditions,

(xxxiv) "PSMA3 " (SEQ ID No:130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA3 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMA3 " nucleic acid or its complement under low stringency conditions,

(xxxv) "PSMA4" (SEQ ID No:131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA4", the variant being encoded by a nucleic acid that hybridizes to the "PSMA4" nucleic acid or its complement under low stringency conditions,

(xxxvi) "PSMA6" (SEQ ID No:132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA6", the variant being encoded by a nucleic acid that hybridizes to the "PSMA6" nucleic acid or its complement under low stringency conditions,

(xxxvii) "PSMB1" (SEQ ID No:133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB1", the variant being encoded by a nucleic acid that hybridizes to the "PSMB1" nucleic acid or its complement under low stringency conditions,

(xxxviii) "PSMB2" (SEQ ID No:134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB2", the variant being encoded by a nucleic acid that hybridizes to the "PSMB2" nucleic acid or its complement under low stringency conditions,

(xxxix) "PSMB3" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB3", the variant being encoded by a nucleic acid that hybridizes to the "PSMB3" nucleic acid or its complement under low stringency conditions,

(xl) "PSMB4 " (SEQ ID No:136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB4 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMB4 " nucleic acid or its complement under low stringency conditions,

(xli) "PSMB5" (SEQ ID No:137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB5", the variant being encoded by a nucleic acid that hybridizes to the "PSMB5" nucleic acid or its complement under low stringency conditions,

(xlii) "PSMB6" (SEQ ID No:138) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB6", the variant being encoded by a nucleic acid that hybridizes to the "PSMB6" nucleic acid or its complement under low stringency conditions,

(xlili) "PSMC1" (SEQ ID No:139) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC1",

the variant being encoded by a nucleic acid that hybridizes to the "PSMC1" nucleic acid or its complement under low stringency conditions,

(xlv) "PSMC2" (SEQ ID No:140) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC2", the variant being encoded by a nucleic acid that hybridizes to the "PSMC2" nucleic acid or its complement under low stringency conditions,

(xlv) "PSMC3" (SEQ ID No:141) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC3", the variant being encoded by a nucleic acid that hybridizes to the "PSMC3" nucleic acid or its complement under low stringency conditions,

(xlvi) "PSMC4" (SEQ ID No:142) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC4", the variant being encoded by a nucleic acid that hybridizes to the "PSMC4" nucleic acid or its complement under low stringency conditions,

(xlvii) "PSMC5" (SEQ ID No:143) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC5", the variant being encoded by a nucleic acid that hybridizes to the "PSMC5" nucleic acid or its complement under low stringency conditions,

(xlviii) "PSMC6" (SEQ ID No:144) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC6", the variant being encoded by a nucleic acid that hybridizes to the "PSMC6" nucleic acid or its complement under low stringency conditions,

(xlix) "PSMD1" (SEQ ID No:145) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD1", the variant being encoded by a nucleic acid that hybridizes to the "PSMD1" nucleic acid or its complement under low stringency conditions,

(l) "PSMD11" (SEQ ID No:146) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD11", the variant being encoded by a nucleic acid that hybridizes to the "PSMD11" nucleic acid or its complement under low stringency conditions,

(li) "PSMD12" (SEQ ID No:147) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD12", the variant being encoded by a nucleic acid that hybridizes to the "PSMD12" nucleic acid or its complement under low stringency conditions,

- (lii) "PSMD13" (SEQ ID No:148) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD13", the variant being encoded by a nucleic acid that hybridizes to the "PSMD13" nucleic acid or its complement under low stringency conditions,
- (liii) "PSMD2" (SEQ ID No:149) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD2", the variant being encoded by a nucleic acid that hybridizes to the "PSMD2" nucleic acid or its complement under low stringency conditions,
- (liv) "PSMD3" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD3", the variant being encoded by a nucleic acid that hybridizes to the "PSMD3" nucleic acid or its complement under low stringency conditions,
- (lv) "PSMD4" (SEQ ID No:151) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD4", the variant being encoded by a nucleic acid that hybridizes to the "PSMD4" nucleic acid or its complement under low stringency conditions,
- (lvi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions,
- (lvii) "Prohibitin" (SEQ ID No:153) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Prohibitin", the variant being encoded by a nucleic acid that hybridizes to the "Prohibitin" nucleic acid or its complement under low stringency conditions,
- (lviii) "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 " (SEQ ID No:154) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 " nucleic acid or its complement under low stringency conditions,
- (lix) "Serine/threonine protein phosphatase 6" (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Serine/threonine protein phosphatase 6", the variant being encoded by a

nucleic acid that hybridizes to the "Serine/threonine protein phosphatase 6" nucleic acid or its complement under low stringency conditions,

(lx) "Sortilin 1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin 1" nucleic acid or its complement under low stringency conditions,

(lxi) "Stearoyl-CoA desaturase " (SEQ ID No:155) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stearoyl-CoA desaturase ", the variant being encoded by a nucleic acid that hybridizes to the "Stearoyl-CoA desaturase " nucleic acid or its complement under low stringency conditions,

(lxii) "Ubiquitin-protein ligase EDD " (SEQ ID No:156) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquitin-protein ligase EDD ", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquitin-protein ligase EDD " nucleic acid or its complement under low stringency conditions,

(lxiii) "Voltage-dependent anion channel 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 2", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 2" nucleic acid or its complement under low stringency conditions,

(lxiv) "Wolframin" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Wolframin", the variant being encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the gamma-secretase activity.

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:

expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Presenilin 2 complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the Presenilin 2 complex selected from

(i) "CGI-51" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-51", the variant being encoded by a nucleic acid that hybridizes to the "CGI-51" nucleic acid or its complement under low stringency conditions,

(ii) "Cerebral protein 10" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein 10", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein 10" nucleic acid or its complement under low stringency conditions,

(iii) "DKFZp586c1924" (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"DKFZp586c1924 ", the variant being encoded by a nucleic acid that hybridizes to the "DKFZp586c1924 " nucleic acid or its complement under low stringency conditions,

(iv) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions,

(v) "FLJ20420" (SEQ ID No:115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20420", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20420" nucleic acid or its complement under low stringency conditions,

(vi) "FLJ22555" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22555", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22555" nucleic acid or its complement under low stringency conditions,

(vii) "FLJ22678" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22678", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22678" nucleic acid or its complement under low stringency conditions,

(viii) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions,

(ix) "KIAA0090" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0090", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,

(x) "KIAA0103" (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0103", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0103" nucleic acid or its complement under low stringency conditions,

(xi) "KIAA1499" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1499", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1499" nucleic acid or its complement under low stringency conditions,

- (xii) "MGC4248 " (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248 ", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248 " nucleic acid or its complement under low stringency conditions, and
- (xiii) "NICE-3" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NICE-3", the variant being encoded by a nucleic acid that hybridizes to the "NICE-3" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising:

- (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
- (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b) or
- (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or

functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container:

- (a) the complex of any of No. 1 - 8 and/or the proteins of No. 13 and/or
- (b) an antibody according to No. 17 and/or
- (c) a nucleic acid encoding a protein of the complex of any of No. 1 - 8 and/or a protein of No. 13 and/or
- (d) cells expressing the complex of any of No. 1 - 8 and/or a protein of No. 13 and, optionally,
- (e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for modifying a physiological substrate of the complex comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "CGI-51" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-51", the variant being encoded by a nucleic acid that hybridizes to the "CGI-51" nucleic acid or its complement under low stringency conditions,
- (ii) "Cerebral protein 10" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein 10", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein 10" nucleic acid or its complement under low stringency conditions,
- (iii) "DKFZp586c1924 " (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DKFZp586c1924 ", the variant being encoded by a nucleic acid that hybridizes to the "DKFZp586c1924 " nucleic acid or its complement under low stringency conditions,
- (iv) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions,
- (v) "FLJ20420" (SEQ ID No:115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20420", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20420" nucleic acid or its complement under low stringency conditions,
- (vi) "FLJ22555" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22555", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22555" nucleic acid or its complement under low stringency conditions,
- (vii) "FLJ22678" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22678", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22678" nucleic acid or its complement under low stringency conditions,
- (viii) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions,

- (ix) "KIAA0090" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0090", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,
- (x) "KIAA0103" (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0103", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0103" nucleic acid or its complement under low stringency conditions,
- (xi) "KIAA1499" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1499", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1499" nucleic acid or its complement under low stringency conditions,
- (xii) "MGC4248 " (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248 ", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248 " nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "NICE-3" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NICE-3", the variant being encoded by a nucleic acid that hybridizes to the "NICE-3" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to a complex of anyone of No. 1 - 8 and/or any of the following the proteins:

- (i) "CGI-51" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-51", the variant being encoded by a nucleic acid that hybridizes to the "CGI-51" nucleic acid or its complement under low stringency conditions,
- (ii) "Cerebral protein 10" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral

protein 10", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein 10" nucleic acid or its complement under low stringency conditions,

(iii) "DKFZp586c1924 " (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"DKFZp586c1924 ", the variant being encoded by a nucleic acid that hybridizes to the "DKFZp586c1924 " nucleic acid or its complement under low stringency conditions,

(iv) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions,

(v) "FLJ20420" (SEQ ID No:115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20420", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20420" nucleic acid or its complement under low stringency conditions,

(vi) "FLJ22555" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22555", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22555" nucleic acid or its complement under low stringency conditions,

(vii) "FLJ22678" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22678", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22678" nucleic acid or its complement under low stringency conditions,

(viii) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions,

(ix) "KIAA0090" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0090", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,

(x) "KIAA0103" (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0103", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0103" nucleic acid or its complement under low stringency conditions,

- (xi) "KIAA1499" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1499", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1499" nucleic acid or its complement under low stringency conditions,
- (xii) "MGC4248 " (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248 ", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248 " nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "NICE-3" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NICE-3", the variant being encoded by a nucleic acid that hybridizes to the "NICE-3" nucleic acid or its complement under low stringency conditions, comprising the steps of:
  - (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and
  - (b) determinig whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:

- (a) exposing said complex, or a cell or organism containing Presenilin 2 complex to one or more candidate molecules; and
- (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether (i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions, and/or

(ii) "200 kDa proteasome activator " (SEQ ID No:99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "200 kDa proteasome activator ", the variant being encoded by a nucleic acid that hybridizes to the "200 kDa proteasome activator " nucleic acid or its complement under low stringency conditions, and/or

(iii) "ADP-ribosylation factor 3" (SEQ ID No:100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADP-ribosylation factor 3", the variant being encoded by a nucleic acid that hybridizes to the "ADP-ribosylation factor 3" nucleic acid or its complement under low stringency conditions, and/or

(iv) "ATP-binding cassette protein, sub-family B, member 1" (SEQ ID No:101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette protein, sub-family B, member 1", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette protein, sub-family B, member 1" nucleic acid or its complement under low stringency conditions, and/or

- (v) "ATP-dependent metalloprotease FtsH1 homologue " (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-dependent metalloprotease FtsH1 homologue ", the variant being encoded by a nucleic acid that hybridizes to the "ATP-dependent metalloprotease FtsH1 homologue " nucleic acid or its complement under low stringency conditions, and/or
- (vi) "Acetolactate synthase " (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Acetolactate synthase ", the variant being encoded by a nucleic acid that hybridizes to the "Acetolactate synthase " nucleic acid or its complement under low stringency conditions, and/or
- (vii) "Adrenoleukodystrophy protein" (SEQ ID No:104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Adrenoleukodystrophy protein", the variant being encoded by a nucleic acid that hybridizes to the "Adrenoleukodystrophy protein" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "CGI-51" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-51", the variant being encoded by a nucleic acid that hybridizes to the "CGI-51" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Calcium-binding protein P22" (SEQ ID No:106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calcium-binding protein P22", the variant being encoded by a nucleic acid that hybridizes to the "Calcium-binding protein P22" nucleic acid or its complement under low stringency conditions, and/or
- (x) "Cation-chloride cotransporter-interacting protein " (SEQ ID No:107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cation-chloride cotransporter-interacting protein ", the variant being encoded by a nucleic acid that hybridizes to the "Cation-chloride cotransporter-interacting protein " nucleic acid or its complement under low stringency conditions, and/or
- (xi) "Centromere/kinetochore protein ZW10 homologue " (SEQ ID No:108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Centromere/kinetochore protein ZW10 homologue ",

the variant being encoded by a nucleic acid that hybridizes to the

"Centromere/kinetochore protein ZW10 homologue " nucleic acid or its complement under low stringency conditions, and/or

(xii) "Cerebral protein 10" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein 10", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein 10" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "DKFZp586c1924 " (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DKFZp586c1924 ", the variant being encoded by a nucleic acid that hybridizes to the "DKFZp586c1924 " nucleic acid or its complement under low stringency conditions, and/or

(xiv) "DOCK3" (SEQ ID No:111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DOCK3", the variant being encoded by a nucleic acid that hybridizes to the "DOCK3" nucleic acid or its complement under low stringency conditions, and/or

(xv) "Down syndrome critical region protein 2" (SEQ ID No:112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Down syndrome critical region protein 2", the variant being encoded by a nucleic acid that hybridizes to the "Down syndrome critical region protein 2" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "ECSIT" (SEQ ID No:113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ECSIT", the variant being encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "FLJ20420" (SEQ ID No:115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20420", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20420" nucleic acid or its complement under low stringency conditions, and/or

- (xix) "FLJ22555" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22555", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22555" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "FLJ22678" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22678", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22678" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" (SEQ ID No:118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3", the variant being encoded by a nucleic acid that hybridizes to the "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "HTRA2" (SEQ ID No:119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HTRA2", the variant being encoded by a nucleic acid that hybridizes to the "HTRA2" nucleic acid or its complement under low stringency conditions, and/or
- (xxiii) "HU-K4 " (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4 ", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4 " nucleic acid or its complement under low stringency conditions, and/or
- (xxiv) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions, and/or
- (xxv) "KIAA0090" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0090", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions, and/or
- (xxvi) "KIAA0103" (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0103", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0103" nucleic acid or its complement under low stringency conditions, and/or

- (xxvii) "KIAA1499" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1499", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1499" nucleic acid or its complement under low stringency conditions, and/or
- (xxviii) "MGC4248 " (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248 ", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248 " nucleic acid or its complement under low stringency conditions, and/or
- (xxix) "NICE-3" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NICE-3", the variant being encoded by a nucleic acid that hybridizes to the "NICE-3" nucleic acid or its complement under low stringency conditions, and/or
- (xxx) "NPD002 " (SEQ ID No:127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NPD002 ", the variant being encoded by a nucleic acid that hybridizes to the "NPD002 " nucleic acid or its complement under low stringency conditions, and/or
- (xxxi) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
- (xxxii) "P63 protein" (SEQ ID No:128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "P63 protein", the variant being encoded by a nucleic acid that hybridizes to the "P63 protein" nucleic acid or its complement under low stringency conditions, and/or
- (xxxiii) "PSMA1 " (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA1 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMA1 " nucleic acid or its complement under low stringency conditions, and/or
- (xxxiv) "PSMA3 " (SEQ ID No:130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA3 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMA3 " nucleic acid or its complement under low stringency conditions, and/or
- (xxxv) "PSMA4" (SEQ ID No:131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA4", the

variant being encoded by a nucleic acid that hybridizes to the "PSMA4" nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "PSMA6" (SEQ ID No:132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA6", the variant being encoded by a nucleic acid that hybridizes to the "PSMA6" nucleic acid or its complement under low stringency conditions, and/or

(xxxvii) "PSMB1" (SEQ ID No:133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB1", the variant being encoded by a nucleic acid that hybridizes to the "PSMB1" nucleic acid or its complement under low stringency conditions, and/or

(xxxviii) "PSMB2" (SEQ ID No:134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB2", the variant being encoded by a nucleic acid that hybridizes to the "PSMB2" nucleic acid or its complement under low stringency conditions, and/or

(xxxix) "PSMB3" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB3", the variant being encoded by a nucleic acid that hybridizes to the "PSMB3" nucleic acid or its complement under low stringency conditions, and/or

(xl) "PSMB4 " (SEQ ID No:136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB4 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMB4 " nucleic acid or its complement under low stringency conditions, and/or

(xli) "PSMB5" (SEQ ID No:137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB5", the variant being encoded by a nucleic acid that hybridizes to the "PSMB5" nucleic acid or its complement under low stringency conditions, and/or

(xlii) "PSMB6" (SEQ ID No:138) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB6", the variant being encoded by a nucleic acid that hybridizes to the "PSMB6" nucleic acid or its complement under low stringency conditions, and/or

(xlili) "PSMC1" (SEQ ID No:139) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC1", the variant being encoded by a nucleic acid that hybridizes to the "PSMC1" nucleic acid or its complement under low stringency conditions, and/or

- (xliv) "PSMC2" (SEQ ID No:140) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC2", the variant being encoded by a nucleic acid that hybridizes to the "PSMC2" nucleic acid or its complement under low stringency conditions, and/or
- (xlv) "PSMC3" (SEQ ID No:141) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC3", the variant being encoded by a nucleic acid that hybridizes to the "PSMC3" nucleic acid or its complement under low stringency conditions, and/or
- (xlvi) "PSMC4" (SEQ ID No:142) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC4", the variant being encoded by a nucleic acid that hybridizes to the "PSMC4" nucleic acid or its complement under low stringency conditions, and/or
- (xlvii) "PSMC5" (SEQ ID No:143) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC5", the variant being encoded by a nucleic acid that hybridizes to the "PSMC5" nucleic acid or its complement under low stringency conditions, and/or
- (xlviii) "PSMC6" (SEQ ID No:144) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC6", the variant being encoded by a nucleic acid that hybridizes to the "PSMC6" nucleic acid or its complement under low stringency conditions, and/or
- (xlix) "PSMD1" (SEQ ID No:145) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD1", the variant being encoded by a nucleic acid that hybridizes to the "PSMD1" nucleic acid or its complement under low stringency conditions, and/or
- (i) "PSMD11" (SEQ ID No:146) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD11", the variant being encoded by a nucleic acid that hybridizes to the "PSMD11" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "PSMD12" (SEQ ID No:147) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD12", the variant being encoded by a nucleic acid that hybridizes to the "PSMD12" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "PSMD13" (SEQ ID No:148) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD13",

the variant being encoded by a nucleic acid that hybridizes to the "PSMD13" nucleic acid or its complement under low stringency conditions, and/or

(liii) "PSMD2" (SEQ ID No:149) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD2", the variant being encoded by a nucleic acid that hybridizes to the "PSMD2" nucleic acid or its complement under low stringency conditions, and/or

(liv) "PSMD3" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD3", the variant being encoded by a nucleic acid that hybridizes to the "PSMD3" nucleic acid or its complement under low stringency conditions, and/or

(lv) "PSMD4" (SEQ ID No:151) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD4", the variant being encoded by a nucleic acid that hybridizes to the "PSMD4" nucleic acid or its complement under low stringency conditions, and/or

(lvi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions, and/or

(lvii) "Prohibitin" (SEQ ID No:153) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Prohibitin", the variant being encoded by a nucleic acid that hybridizes to the "Prohibitin" nucleic acid or its complement under low stringency conditions, and/or

(lviii) "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 " (SEQ ID No:154) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 " nucleic acid or its complement under low stringency conditions, and/or

(lix) "Serine/threonine protein phosphatase 6" (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Serine/threonine protein phosphatase 6", the variant being encoded by a nucleic acid that hybridizes to the "Serine/threonine protein phosphatase 6" nucleic acid or its complement under low stringency conditions, and/or

(Ix) "Sortilin 1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin 1" nucleic acid or its complement under low stringency conditions, and/or

(Ixi) "Stearoyl-CoA desaturase " (SEQ ID No:155) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stearoyl-CoA desaturase ", the variant being encoded by a nucleic acid that hybridizes to the "Stearoyl-CoA desaturase " nucleic acid or its complement under low stringency conditions, and/or

(Ixi) "Ubiquitin-protein ligase EDD " (SEQ ID No:156) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquitin-protein ligase EDD ", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquitin-protein ligase EDD " nucleic acid or its complement under low stringency conditions, and/or

(Ixi) "Voltage-dependent anion channel 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 2", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 2" nucleic acid or its complement under low stringency conditions, and/or

(Ixiv) "Wolframin" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Wolframin", the variant being encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether

- (i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions, and/or
- (ii) "200 kDa proteasome activator " (SEQ ID No:99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "200 kDa proteasome activator ", the variant being encoded by a nucleic acid that hybridizes to the "200 kDa proteasome activator " nucleic acid or its complement under low stringency conditions, and/or
- (iii) "ADP-ribosylation factor 3" (SEQ ID No:100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADP-ribosylation factor 3", the variant being encoded by a nucleic acid that hybridizes to the "ADP-ribosylation factor 3" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "ATP-binding cassette protein, sub-family B, member 1" (SEQ ID No:101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette protein, sub-family B, member 1", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette protein, sub-family B, member 1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "ATP-dependent metalloprotease FtsH1 homologue " (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-dependent metalloprotease FtsH1 homologue ", the variant being encoded by a nucleic acid that hybridizes to the "ATP-dependent metalloprotease FtsH1 homologue " nucleic acid or its complement under low stringency conditions, and/or
- (vi) "Acetolactate synthase " (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Acetolactate synthase ", the variant being encoded by a nucleic acid that hybridizes to the "Acetolactate synthase " nucleic acid or its complement under low stringency conditions, and/or
- (vii) "Adrenoleukodystrophy protein" (SEQ ID No:104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Adrenoleukodystrophy protein", the variant being encoded by a nucleic acid that hybridizes to the "Adrenoleukodystrophy protein" nucleic acid or its complement under low stringency conditions, and/or

(viii) "CGI-51" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-51", the variant being encoded by a nucleic acid that hybridizes to the "CGI-51" nucleic acid or its complement under low stringency conditions, and/or

(ix) "Calcium-binding protein P22" (SEQ ID No:106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calcium-binding protein P22", the variant being encoded by a nucleic acid that hybridizes to the "Calcium-binding protein P22" nucleic acid or its complement under low stringency conditions, and/or

(x) "Cation-chloride cotransporter-interacting protein " (SEQ ID No:107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cation-chloride cotransporter-interacting protein ", the variant being encoded by a nucleic acid that hybridizes to the "Cation-chloride cotransporter-interacting protein " nucleic acid or its complement under low stringency conditions, and/or

(xi) "Centromere/kinetochore protein ZW10 homologue " (SEQ ID No:108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Centromere/kinetochore protein ZW10 homologue ", the variant being encoded by a nucleic acid that hybridizes to the "Centromere/kinetochore protein ZW10 homologue " nucleic acid or its complement under low stringency conditions, and/or

(xii) "Cerebral protein 10" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein 10", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein 10" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "DKFZp586c1924 " (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DKFZp586c1924 ", the variant being encoded by a nucleic acid that hybridizes to the "DKFZp586c1924 " nucleic acid or its complement under low stringency conditions, and/or

- (xiv) "DOCK3" (SEQ ID No:111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DOCK3", the variant being encoded by a nucleic acid that hybridizes to the "DOCK3" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "Down syndrome critical region protein 2" (SEQ ID No:112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Down syndrome critical region protein 2", the variant being encoded by a nucleic acid that hybridizes to the "Down syndrome critical region protein 2" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "ECSIT" (SEQ ID No:113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ECSIT", the variant being encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "FLJ20420" (SEQ ID No:115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20420", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20420" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "FLJ22555" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22555", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22555" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "FLJ22678" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22678", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22678" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" (SEQ ID No:118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3", the variant being encoded by a nucleic acid that

hybridizes to the "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "HTRA2" (SEQ ID No:119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HTRA2", the variant being encoded by a nucleic acid that hybridizes to the "HTRA2" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "HU-K4 " (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4 ", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4 " nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "KIAA0090" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0090", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "KIAA0103" (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0103", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0103" nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "KIAA1499" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1499", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1499" nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "MGC4248 " (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248 ", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248 " nucleic acid or its complement under low stringency conditions, and/or

(xxix) "NICE-3" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NICE-3", the variant being encoded by a nucleic acid that hybridizes to the "NICE-3" nucleic acid or its complement under low stringency conditions, and/or

(xxx) "NPD002 " (SEQ ID No:127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NPD002 ", the variant being encoded by a nucleic acid that hybridizes to the "NPD002 " nucleic acid or its complement under low stringency conditions, and/or

(xxxi) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(xxxii) "P63 protein" (SEQ ID No:128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "P63 protein", the variant being encoded by a nucleic acid that hybridizes to the "P63 protein" nucleic acid or its complement under low stringency conditions, and/or

(xxxiii) "PSMA1 " (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA1 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMA1 " nucleic acid or its complement under low stringency conditions, and/or

(xxxiv) "PSMA3 " (SEQ ID No:130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA3 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMA3 " nucleic acid or its complement under low stringency conditions, and/or

(xxxv) "PSMA4" (SEQ ID No:131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA4", the variant being encoded by a nucleic acid that hybridizes to the "PSMA4" nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "PSMA6" (SEQ ID No:132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA6", the variant being encoded by a nucleic acid that hybridizes to the "PSMA6" nucleic acid or its complement under low stringency conditions, and/or

(xxxvii) "PSMB1" (SEQ ID No:133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB1", the variant being encoded by a nucleic acid that hybridizes to the "PSMB1" nucleic acid or its complement under low stringency conditions, and/or

(xxxviii) "PSMB2" (SEQ ID No:134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB2", the

variant being encoded by a nucleic acid that hybridizes to the "PSMB2" nucleic acid or its complement under low stringency conditions, and/or

(xxxix) "PSMB3" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB3", the variant being encoded by a nucleic acid that hybridizes to the "PSMB3" nucleic acid or its complement under low stringency conditions, and/or

(xli) "PSMB4 " (SEQ ID No:136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB4 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMB4 " nucleic acid or its complement under low stringency conditions, and/or

(xlii) "PSMB5" (SEQ ID No:137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB5", the variant being encoded by a nucleic acid that hybridizes to the "PSMB5" nucleic acid or its complement under low stringency conditions, and/or

(xlii) "PSMB6" (SEQ ID No:138) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB6", the variant being encoded by a nucleic acid that hybridizes to the "PSMB6" nucleic acid or its complement under low stringency conditions, and/or

(xlili) "PSMC1" (SEQ ID No:139) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC1", the variant being encoded by a nucleic acid that hybridizes to the "PSMC1" nucleic acid or its complement under low stringency conditions, and/or

(xliv) "PSMC2" (SEQ ID No:140) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC2", the variant being encoded by a nucleic acid that hybridizes to the "PSMC2" nucleic acid or its complement under low stringency conditions, and/or

(xlv) "PSMC3" (SEQ ID No:141) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC3", the variant being encoded by a nucleic acid that hybridizes to the "PSMC3" nucleic acid or its complement under low stringency conditions, and/or

(xlvi) "PSMC4" (SEQ ID No:142) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC4", the variant being encoded by a nucleic acid that hybridizes to the "PSMC4" nucleic acid or its complement under low stringency conditions, and/or

(xlvii) "PSMC5" (SEQ ID No:143) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC5", the variant being encoded by a nucleic acid that hybridizes to the "PSMC5" nucleic acid or its complement under low stringency conditions, and/or

(xlviii) "PSMC6" (SEQ ID No:144) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC6", the variant being encoded by a nucleic acid that hybridizes to the "PSMC6" nucleic acid or its complement under low stringency conditions, and/or

(xlix) "PSMD1" (SEQ ID No:145) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD1", the variant being encoded by a nucleic acid that hybridizes to the "PSMD1" nucleic acid or its complement under low stringency conditions, and/or

(l) "PSMD11" (SEQ ID No:146) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD11", the variant being encoded by a nucleic acid that hybridizes to the "PSMD11" nucleic acid or its complement under low stringency conditions, and/or

(li) "PSMD12" (SEQ ID No:147) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD12", the variant being encoded by a nucleic acid that hybridizes to the "PSMD12" nucleic acid or its complement under low stringency conditions, and/or

(lii) "PSMD13" (SEQ ID No:148) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD13", the variant being encoded by a nucleic acid that hybridizes to the "PSMD13" nucleic acid or its complement under low stringency conditions, and/or

(liii) "PSMD2" (SEQ ID No:149) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD2", the variant being encoded by a nucleic acid that hybridizes to the "PSMD2" nucleic acid or its complement under low stringency conditions, and/or

(liv) "PSMD3" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD3", the variant being encoded by a nucleic acid that hybridizes to the "PSMD3" nucleic acid or its complement under low stringency conditions, and/or

(lv) "PSMD4" (SEQ ID No:151) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD4", the variant

being encoded by a nucleic acid that hybridizes to the "PSMD4" nucleic acid or its complement under low stringency conditions, and/or

(lvi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions, and/or

(lvii) "Prohibitin" (SEQ ID No:153) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Prohibitin", the variant being encoded by a nucleic acid that hybridizes to the "Prohibitin" nucleic acid or its complement under low stringency conditions, and/or

(lviii) "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 " (SEQ ID No:154) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 " nucleic acid or its complement under low stringency conditions, and/or

(lix) "Serine/threonine protein phosphatase 6" (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Serine/threonine protein phosphatase 6", the variant being encoded by a nucleic acid that hybridizes to the "Serine/threonine protein phosphatase 6" nucleic acid or its complement under low stringency conditions, and/or

(lx) "Sortilin 1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin 1" nucleic acid or its complement under low stringency conditions, and/or

(lxi) "Stearoyl-CoA desaturase " (SEQ ID No:155) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stearoyl-CoA desaturase ", the variant being encoded by a nucleic acid that hybridizes to the "Stearoyl-CoA desaturase " nucleic acid or its complement under low stringency conditions, and/or

(lxii) "Ubiquitin-protein ligase EDD " (SEQ ID No:156) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquitin-protein ligase EDD ", the variant being encoded by a nucleic acid that

hybridizes to the "Ubiquitin-protein ligase EDD " nucleic acid or its complement under low stringency conditions, and/or

(lxiii) "Voltage-dependent anion channel 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 2", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 2" nucleic acid or its complement under low stringency conditions, and/or

(lxiv) "Wolframin" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Wolframin", the variant being encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the gamma-secretase activity of, or protein composition of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins:

(i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a

nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(ii) "200 kDa proteasome activator " (SEQ ID No:99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "200 kDa proteasome activator ", the variant being encoded by a nucleic acid that hybridizes to the "200 kDa proteasome activator " nucleic acid or its complement under low stringency conditions,

(iii) "ADP-ribosylation factor 3" (SEQ ID No:100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADP-ribosylation factor 3", the variant being encoded by a nucleic acid that hybridizes to the "ADP-ribosylation factor 3" nucleic acid or its complement under low stringency conditions,

(iv) "ATP-binding cassette protein, sub-family B, member 1" (SEQ ID No:101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette protein, sub-family B, member 1", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette protein, sub-family B, member 1" nucleic acid or its complement under low stringency conditions,

(v) "ATP-dependent metalloprotease FtsH1 homologue " (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-dependent metalloprotease FtsH1 homologue ", the variant being encoded by a nucleic acid that hybridizes to the "ATP-dependent metalloprotease FtsH1 homologue " nucleic acid or its complement under low stringency conditions,

(vi) "Acetolactate synthase " (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Acetolactate synthase ", the variant being encoded by a nucleic acid that hybridizes to the "Acetolactate synthase " nucleic acid or its complement under low stringency conditions,

(vii) "Adrenoleukodystrophy protein" (SEQ ID No:104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Adrenoleukodystrophy protein", the variant being encoded by a nucleic acid that hybridizes to the "Adrenoleukodystrophy protein" nucleic acid or its complement under low stringency conditions,

(viii) "CGI-51" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-51", the variant being encoded by a nucleic acid that hybridizes to the "CGI-51" nucleic acid or its complement under low stringency conditions,

(ix) "Calcium-binding protein P22" (SEQ ID No:106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calcium-binding protein P22", the variant being encoded by a nucleic acid that hybridizes to the "Calcium-binding protein P22" nucleic acid or its complement under low stringency conditions,

(x) "Cation-chloride cotransporter-interacting protein " (SEQ ID No:107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cation-chloride cotransporter-interacting protein ", the variant being encoded by a nucleic acid that hybridizes to the "Cation-chloride cotransporter-interacting protein " nucleic acid or its complement under low stringency conditions,

(xi) "Centromere/kinetochore protein ZW10 homologue " (SEQ ID No:108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Centromere/kinetochore protein ZW10 homologue ", the variant being encoded by a nucleic acid that hybridizes to the "Centromere/kinetochore protein ZW10 homologue " nucleic acid or its complement under low stringency conditions,

(xii) "Cerebral protein 10" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein 10", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein 10" nucleic acid or its complement under low stringency conditions,

(xiii) "DKFZp586c1924 " (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DKFZp586c1924 ", the variant being encoded by a nucleic acid that hybridizes to the "DKFZp586c1924 " nucleic acid or its complement under low stringency conditions,

(xiv) "DOCK3" (SEQ ID No:111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DOCK3", the variant being encoded by a nucleic acid that hybridizes to the "DOCK3" nucleic acid or its complement under low stringency conditions,

(xv) "Down syndrome critical region protein 2" (SEQ ID No:112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a

variant of "Down syndrome critical region protein 2", the variant being encoded by a nucleic acid that hybridizes to the "Down syndrome critical region protein 2" nucleic acid or its complement under low stringency conditions,

(xvi) "ECSIT" (SEQ ID No:113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ECSIT", the variant being encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(xvii) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions,

(xviii) "FLJ20420" (SEQ ID No:115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20420", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20420" nucleic acid or its complement under low stringency conditions,

(xix) "FLJ22555" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22555", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22555" nucleic acid or its complement under low stringency conditions,

(xx) "FLJ22678" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22678", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22678" nucleic acid or its complement under low stringency conditions,

(xxi) "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" (SEQ ID No:118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3", the variant being encoded by a nucleic acid that hybridizes to the "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" nucleic acid or its complement under low stringency conditions,

(xxii) "HTRA2" (SEQ ID No:119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HTRA2", the variant being encoded by a nucleic acid that hybridizes to the "HTRA2" nucleic acid or its complement under low stringency conditions,

- (xxiii) "HU-K4 " (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4 ", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4 " nucleic acid or its complement under low stringency conditions,
- (xxiv) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions,
- (xxv) "KIAA0090" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0090", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,
- (xxvi) "KIAA0103" (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0103", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0103" nucleic acid or its complement under low stringency conditions,
- (xxvii) "KIAA1499" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1499", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1499" nucleic acid or its complement under low stringency conditions,
- (xxviii) "MGC4248 " (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248 ", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248 " nucleic acid or its complement under low stringency conditions,
- (xxix) "NICE-3" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NICE-3", the variant being encoded by a nucleic acid that hybridizes to the "NICE-3" nucleic acid or its complement under low stringency conditions,
- (xxx) "NPD002 " (SEQ ID No:127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NPD002 ", the variant being encoded by a nucleic acid that hybridizes to the "NPD002 " nucleic acid or its complement under low stringency conditions,
- (xxxi) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin",

the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(xxxii) "P63 protein" (SEQ ID No:128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "P63 protein", the variant being encoded by a nucleic acid that hybridizes to the "P63 protein" nucleic acid or its complement under low stringency conditions,

(xxxiii) "PSMA1 " (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA1 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMA1 " nucleic acid or its complement under low stringency conditions,

(xxxiv) "PSMA3 " (SEQ ID No:130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA3 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMA3 " nucleic acid or its complement under low stringency conditions,

(xxxv) "PSMA4" (SEQ ID No:131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA4", the variant being encoded by a nucleic acid that hybridizes to the "PSMA4" nucleic acid or its complement under low stringency conditions,

(xxxvi) "PSMA6" (SEQ ID No:132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMA6", the variant being encoded by a nucleic acid that hybridizes to the "PSMA6" nucleic acid or its complement under low stringency conditions,

(xxxvii) "PSMB1" (SEQ ID No:133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB1", the variant being encoded by a nucleic acid that hybridizes to the "PSMB1" nucleic acid or its complement under low stringency conditions,

(xxxviii) "PSMB2" (SEQ ID No:134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB2", the variant being encoded by a nucleic acid that hybridizes to the "PSMB2" nucleic acid or its complement under low stringency conditions,

(xxxix) "PSMB3" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB3", the variant being encoded by a nucleic acid that hybridizes to the "PSMB3" nucleic acid or its complement under low stringency conditions,

(xi) "PSMB4 " (SEQ ID No:136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB4 ", the variant being encoded by a nucleic acid that hybridizes to the "PSMB4 " nucleic acid or its complement under low stringency conditions,

(xli) "PSMB5" (SEQ ID No:137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB5", the variant being encoded by a nucleic acid that hybridizes to the "PSMB5" nucleic acid or its complement under low stringency conditions,

(xlii) "PSMB6" (SEQ ID No:138) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMB6", the variant being encoded by a nucleic acid that hybridizes to the "PSMB6" nucleic acid or its complement under low stringency conditions,

(xlili) "PSMC1" (SEQ ID No:139) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC1", the variant being encoded by a nucleic acid that hybridizes to the "PSMC1" nucleic acid or its complement under low stringency conditions,

(xliv) "PSMC2" (SEQ ID No:140) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC2", the variant being encoded by a nucleic acid that hybridizes to the "PSMC2" nucleic acid or its complement under low stringency conditions,

(xlv) "PSMC3" (SEQ ID No:141) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC3", the variant being encoded by a nucleic acid that hybridizes to the "PSMC3" nucleic acid or its complement under low stringency conditions,

(xlvi) "PSMC4" (SEQ ID No:142) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC4", the variant being encoded by a nucleic acid that hybridizes to the "PSMC4" nucleic acid or its complement under low stringency conditions,

(xlvii) "PSMC5" (SEQ ID No:143) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC5", the variant being encoded by a nucleic acid that hybridizes to the "PSMC5" nucleic acid or its complement under low stringency conditions,

(xlviii) "PSMC6" (SEQ ID No:144) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMC6",

the variant being encoded by a nucleic acid that hybridizes to the "PSMC6" nucleic acid or its complement under low stringency conditions,

(xlix) "PSMD1" (SEQ ID No:145) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD1", the variant being encoded by a nucleic acid that hybridizes to the "PSMD1" nucleic acid or its complement under low stringency conditions,

(l) "PSMD11" (SEQ ID No:146) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD11", the variant being encoded by a nucleic acid that hybridizes to the "PSMD11" nucleic acid or its complement under low stringency conditions,

(li) "PSMD12" (SEQ ID No:147) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD12", the variant being encoded by a nucleic acid that hybridizes to the "PSMD12" nucleic acid or its complement under low stringency conditions,

(lii) "PSMD13" (SEQ ID No:148) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD13", the variant being encoded by a nucleic acid that hybridizes to the "PSMD13" nucleic acid or its complement under low stringency conditions,

(liii) "PSMD2" (SEQ ID No:149) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD2", the variant being encoded by a nucleic acid that hybridizes to the "PSMD2" nucleic acid or its complement under low stringency conditions,

(liv) "PSMD3" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD3", the variant being encoded by a nucleic acid that hybridizes to the "PSMD3" nucleic acid or its complement under low stringency conditions,

(lv) "PSMD4" (SEQ ID No:151) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PSMD4", the variant being encoded by a nucleic acid that hybridizes to the "PSMD4" nucleic acid or its complement under low stringency conditions,

(lvi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions,

(lvii) "Prohibitin" (SEQ ID No:153) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Prohibitin", the variant being encoded by a nucleic acid that hybridizes to the "Prohibitin" nucleic acid or its complement under low stringency conditions,

(lviii) "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 " (SEQ ID No:154) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3 " nucleic acid or its complement under low stringency conditions,

(lix) "Serine/threonine protein phosphatase 6" (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Serine/threonine protein phosphatase 6", the variant being encoded by a nucleic acid that hybridizes to the "Serine/threonine protein phosphatase 6" nucleic acid or its complement under low stringency conditions,

(lx) "Sortilin 1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sortilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sortilin 1" nucleic acid or its complement under low stringency conditions,

(lxi) "Stearoyl-CoA desaturase " (SEQ ID No:155) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stearoyl-CoA desaturase ", the variant being encoded by a nucleic acid that hybridizes to the "Stearoyl-CoA desaturase " nucleic acid or its complement under low stringency conditions,

(lxii) "Ubiquitin-protein ligase EDD " (SEQ ID No:156) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Ubiquitin-protein ligase EDD ", the variant being encoded by a nucleic acid that hybridizes to the "Ubiquitin-protein ligase EDD " nucleic acid or its complement under low stringency conditions,

(lxiii) "Voltage-dependent anion channel 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 2", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 2" nucleic acid or its complement under low stringency conditions, and/or (lxiv) "Wolframin" (SEQ ID No:158)

or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Wolframin", the variant being encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

The invention further relates to the Nicastrin complex:

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,
    - (ii) "BACE1" (SEQ ID No:161) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BACE1", the variant being encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,
    - (iii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
    - (iv) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,
    - (v) "Presenilin-1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin-1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin-1" nucleic acid or its complement under low stringency conditions, and

(vi) "Presenilin-2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin-2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin-2" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

(i) "18 kDa microsomal signal peptidase subunit" (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit" nucleic acid or its complement under low stringency conditions,

(ii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(iii) "ATP-binding cassette, sub-family A, member 3" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette, sub-family A, member 3", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette, sub-family A, member 3" nucleic acid or its complement under low stringency conditions,

(iv) "BSCv protein" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BSCv protein", the variant being encoded by a nucleic acid that hybridizes to the "BSCv protein" nucleic acid or its complement under low stringency conditions,

(v) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,

(vi) "Casein kinase II beta chain " (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Casein kinase II beta chain ", the variant being encoded by a nucleic acid that hybridizes to the "Casein kinase II beta chain " nucleic acid or its complement under low stringency conditions,

- (vii) "Cathepsin B" (SEQ ID No:165) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cathepsin B", the variant being encoded by a nucleic acid that hybridizes to the "Cathepsin B" nucleic acid or its complement under low stringency conditions,
- (viii) "Delta-6 fatty acid desaturase " (SEQ ID No:166) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-6 fatty acid desaturase ", the variant being encoded by a nucleic acid that hybridizes to the "Delta-6 fatty acid desaturase " nucleic acid or its complement under low stringency conditions,
- (ix) "ENSG00000144840" (SEQ ID No:167) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENSG00000144840", the variant being encoded by a nucleic acid that hybridizes to the "ENSG00000144840" nucleic acid or its complement under low stringency conditions,
- (x) "FLJ13977" (SEQ ID No:168) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13977", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13977" nucleic acid or its complement under low stringency conditions,
- (xi) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions,
- (xii) "FLJ20481" (SEQ ID No:169) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20481", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xiii) "FLJ22390" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22390", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22390" nucleic acid or its complement under low stringency conditions,
- (xiv) "Hypothetical protein tyrosine phosphatase ensg00000149185 " (SEQ ID No:171) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Hypothetical protein tyrosine phosphatase ensg00000149185 ", the variant being encoded by a nucleic acid that hybridizes to the

"Hypothetical protein tyrosine phosphatase ensg00000149185 " nucleic acid or its complement under low stringency conditions,

(xv) "ICAM-2" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ICAM-2", the variant being encoded by a nucleic acid that hybridizes to the "ICAM-2" nucleic acid or its complement under low stringency conditions,

(xvi) "KIAA1181" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1181", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1181" nucleic acid or its complement under low stringency conditions,

(xvii) "KIAA1533" (SEQ ID No:174) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1533", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1533" nucleic acid or its complement under low stringency conditions,

(xviii) "Mesenchymal stem cell protein DSCD75 " (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Mesenchymal stem cell protein DSCD75 ", the variant being encoded by a nucleic acid that hybridizes to the "Mesenchymal stem cell protein DSCD75 " nucleic acid or its complement under low stringency conditions,

(xix) "NICE-3" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NICE-3", the variant being encoded by a nucleic acid that hybridizes to the "NICE-3" nucleic acid or its complement under low stringency conditions,

(xx) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xxi) "PP1, regulatory subunit 15B " (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP1, regulatory subunit 15B ", the variant being encoded by a nucleic acid that hybridizes to the "PP1, regulatory subunit 15B " nucleic acid or its complement under low stringency conditions,

(xxii) "Protein amplified in osteosarcoma (OS-9)" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue

thereof, or a variant of "Protein amplified in osteosarcoma (OS-9)", the variant being encoded by a nucleic acid that hybridizes to the "Protein amplified in osteosarcoma (OS-9)" nucleic acid or its complement under low stringency conditions,

(xxiii) "Protein similar to stromal cell-derived factor 2 " (SEQ ID No:179) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to stromal cell-derived factor 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to stromal cell-derived factor 2 " nucleic acid or its complement under low stringency conditions,

(xxiv) "Protocadherin beta 8 " (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8 " nucleic acid or its complement under low stringency conditions,

(xxv) "REP8 protein " (SEQ ID No:181) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "REP8 protein ", the variant being encoded by a nucleic acid that hybridizes to the "REP8 protein " nucleic acid or its complement under low stringency conditions,

(xxvi) "RING finger protein 5 " (SEQ ID No:182) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RING finger protein 5 ", the variant being encoded by a nucleic acid that hybridizes to the "RING finger protein 5 " nucleic acid or its complement under low stringency conditions,

(xxvii) "Retinal short-chain dehydrogenase/reductase retSDR2 " (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Retinal short-chain dehydrogenase/reductase retSDR2 ", the variant being encoded by a nucleic acid that hybridizes to the "Retinal short-chain dehydrogenase/reductase retSDR2 " nucleic acid or its complement under low stringency conditions,

(xxviii) "Stromal cell-derived factor 2-like 1 " (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stromal cell-derived factor 2-like 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Stromal cell-derived factor 2-like 1 " nucleic acid or its complement under low stringency conditions,

(xxix) "Thioredoxin domain-containing protein" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a

variant of "Thioredoxin domain-containing protein", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, and

(xxx) "Voltage-dependent anion channel 1" (SEQ ID No:186) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 1", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. The protein complex according to No. 1 wherein the first protein is the protein "Nicastrin" (SEQ ID No:14), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid under low stringency conditions.

3. The protein complex according to No. 1 comprising the following proteins:

(i) "18 kDa microsomal signal peptidase subunit" (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit" nucleic acid or its complement under low stringency conditions,

(ii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

- (iii) "ATP-binding cassette, sub-family A, member 3" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette, sub-family A, member 3", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette, sub-family A, member 3" nucleic acid or its complement under low stringency conditions,
- (iv) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,
- (v) "BACE1" (SEQ ID No:161) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BACE1", the variant being encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,
- (vi) "BSCv protein" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BSCv protein", the variant being encoded by a nucleic acid that hybridizes to the "BSCv protein" nucleic acid or its complement under low stringency conditions,
- (vii) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,
- (viii) "Casein kinase II beta chain " (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Casein kinase II beta chain ", the variant being encoded by a nucleic acid that hybridizes to the "Casein kinase II beta chain " nucleic acid or its complement under low stringency conditions,
- (ix) "Cathepsin B" (SEQ ID No:165) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cathepsin B", the variant being encoded by a nucleic acid that hybridizes to the "Cathepsin B" nucleic acid or its complement under low stringency conditions,
- (x) "Delta-6 fatty acid desaturase " (SEQ ID No:166) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-6 fatty acid desaturase ", the variant being encoded by a nucleic acid that

hybridizes to the "Delta-6 fatty acid desaturase " nucleic acid or its complement under low stringency conditions,

(xi) "ENSG00000144840" (SEQ ID No:167) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENSG00000144840", the variant being encoded by a nucleic acid that hybridizes to the "ENSG00000144840" nucleic acid or its complement under low stringency conditions,

(xii) "FLJ13977" (SEQ ID No:168) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13977", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13977" nucleic acid or its complement under low stringency conditions,

(xiii) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions,

(xiv) "FLJ20481" (SEQ ID No:169) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20481", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(xv) "FLJ22390" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22390", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22390" nucleic acid or its complement under low stringency conditions,

(xvi) "Hypothetical protein tyrosine phosphatase ensg00000149185 " (SEQ ID No:171) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Hypothetical protein tyrosine phosphatase ensg00000149185 ", the variant being encoded by a nucleic acid that hybridizes to the "Hypothetical protein tyrosine phosphatase ensg00000149185 " nucleic acid or its complement under low stringency conditions,

(xvii) "ICAM-2" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ICAM-2", the variant being encoded by a nucleic acid that hybridizes to the "ICAM-2" nucleic acid or its complement under low stringency conditions,

(xviii) "KIAA1181" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1181",

the variant being encoded by a nucleic acid that hybridizes to the "KIAA1181" nucleic acid or its complement under low stringency conditions,

(xix) "KIAA1533" (SEQ ID No:174) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1533", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1533" nucleic acid or its complement under low stringency conditions,

(xx) "Mesenchymal stem cell protein DSCD75 " (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Mesenchymal stem cell protein DSCD75 ", the variant being encoded by a nucleic acid that hybridizes to the "Mesenchymal stem cell protein DSCD75 " nucleic acid or its complement under low stringency conditions,

(xxi) "NICE-3" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NICE-3", the variant being encoded by a nucleic acid that hybridizes to the "NICE-3" nucleic acid or its complement under low stringency conditions,

(xxii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xxiii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(xxiv) "PP1, regulatory subunit 15B " (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP1, regulatory subunit 15B ", the variant being encoded by a nucleic acid that hybridizes to the "PP1, regulatory subunit 15B " nucleic acid or its complement under low stringency conditions,

(xxv) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,

(xxvi) "Presenilin-1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin-

1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin-1" nucleic acid or its complement under low stringency conditions,

(xxvii) "Presenilin-2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin-2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin-2" nucleic acid or its complement under low stringency conditions,

(xxviii) "Protein amplified in osteosarcoma (OS-9)" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein amplified in osteosarcoma (OS-9)", the variant being encoded by a nucleic acid that hybridizes to the "Protein amplified in osteosarcoma (OS-9)" nucleic acid or its complement under low stringency conditions,

(xxix) "Protein similar to stromal cell-derived factor 2 " (SEQ ID No:179) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to stromal cell-derived factor 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to stromal cell-derived factor 2 " nucleic acid or its complement under low stringency conditions,

(xxx) "Protocadherin beta 8 " (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8 " nucleic acid or its complement under low stringency conditions,

(xxxi) "REP8 protein " (SEQ ID No:181) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "REP8 protein ", the variant being encoded by a nucleic acid that hybridizes to the "REP8 protein " nucleic acid or its complement under low stringency conditions,

(xxxii) "RING finger protein 5 " (SEQ ID No:182) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RING finger protein 5 ", the variant being encoded by a nucleic acid that hybridizes to the "RING finger protein 5 " nucleic acid or its complement under low stringency conditions,

(xxxiii) "Retinal short-chain dehydrogenase/reductase retSDR2 " (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Retinal short-chain dehydrogenase/reductase retSDR2 ", the variant being encoded by a nucleic acid that hybridizes to the "Retinal

short-chain dehydrogenase/reductase retSDR2 " nucleic acid or its complement under low stringency conditions,

(xxxiv) "Stromal cell-derived factor 2-like 1 " (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stromal cell-derived factor 2-like 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Stromal cell-derived factor 2-like 1 " nucleic acid or its complement under low stringency conditions,

(xxxv) "Thioredoxin domain-containing protein" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "Voltage-dependent anion channel 1" (SEQ ID No:186) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 1", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising at least 7 but no more than 35 of the following proteins:

(i) "18 kDa microsomal signal peptidase subunit" (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit" nucleic acid or its complement under low stringency conditions,

(ii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(iii) "ATP-binding cassette, sub-family A, member 3" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette, sub-family A, member 3", the variant being

encoded by a nucleic acid that hybridizes to the "ATP-binding cassette, sub-family A, member 3" nucleic acid or its complement under low stringency conditions,

(iv) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,

(v) "BACE1" (SEQ ID No:161) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BACE1", the variant being encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,

(vi) "BSCv protein" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BSCv protein", the variant being encoded by a nucleic acid that hybridizes to the "BSCv protein" nucleic acid or its complement under low stringency conditions,

(vii) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,

(viii) "Casein kinase II beta chain " (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Casein kinase II beta chain ", the variant being encoded by a nucleic acid that hybridizes to the "Casein kinase II beta chain " nucleic acid or its complement under low stringency conditions,

(ix) "Cathepsin B" (SEQ ID No:165) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cathepsin B", the variant being encoded by a nucleic acid that hybridizes to the "Cathepsin B" nucleic acid or its complement under low stringency conditions,

(x) "Delta-6 fatty acid desaturase " (SEQ ID No:166) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-6 fatty acid desaturase ", the variant being encoded by a nucleic acid that hybridizes to the "Delta-6 fatty acid desaturase " nucleic acid or its complement under low stringency conditions,

(xi) "ENSG00000144840" (SEQ ID No:167) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

- "ENSG00000144840", the variant being encoded by a nucleic acid that hybridizes to the "ENSG00000144840" nucleic acid or its complement under low stringency conditions,
- (xii) "FLJ13977" (SEQ ID No:168) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13977", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13977" nucleic acid or its complement under low stringency conditions,
- (xiii) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions,
- (xiv) "FLJ20481" (SEQ ID No:169) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20481", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xv) "FLJ22390" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22390", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22390" nucleic acid or its complement under low stringency conditions,
- (xvi) "Hypothetical protein tyrosine phosphatase ensg00000149185 " (SEQ ID No:171) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Hypothetical protein tyrosine phosphatase ensg00000149185 ", the variant being encoded by a nucleic acid that hybridizes to the "Hypothetical protein tyrosine phosphatase ensg00000149185 " nucleic acid or its complement under low stringency conditions,
- (xvii) "ICAM-2" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ICAM-2", the variant being encoded by a nucleic acid that hybridizes to the "ICAM-2" nucleic acid or its complement under low stringency conditions,
- (xviii) "KIAA1181" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1181", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1181" nucleic acid or its complement under low stringency conditions,
- (xix) "KIAA1533" (SEQ ID No:174) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1533",

the variant being encoded by a nucleic acid that hybridizes to the "KIAA1533" nucleic acid or its complement under low stringency conditions,

(xx) "Mesenchymal stem cell protein DSCD75 " (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Mesenchymal stem cell protein DSCD75 ", the variant being encoded by a nucleic acid that hybridizes to the "Mesenchymal stem cell protein DSCD75 " nucleic acid or its complement under low stringency conditions,

(xxi) "NICE-3" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NICE-3", the variant being encoded by a nucleic acid that hybridizes to the "NICE-3" nucleic acid or its complement under low stringency conditions,

(xxii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xxiii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(xxiv) "PP1, regulatory subunit 15B " (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP1, regulatory subunit 15B ", the variant being encoded by a nucleic acid that hybridizes to the "PP1, regulatory subunit 15B " nucleic acid or its complement under low stringency conditions,

(xxv) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,

(xxvi) "Presenilin-1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin-1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin-1" nucleic acid or its complement under low stringency conditions,

(xxvii) "Presenilin-2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin-

2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin-2" nucleic acid or its complement under low stringency conditions,

(xxviii) "Protein amplified in osteosarcoma (OS-9)" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein amplified in osteosarcoma (OS-9)", the variant being encoded by a nucleic acid that hybridizes to the "Protein amplified in osteosarcoma (OS-9)" nucleic acid or its complement under low stringency conditions,

(xxix) "Protein similar to stromal cell-derived factor 2 " (SEQ ID No:179) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to stromal cell-derived factor 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to stromal cell-derived factor 2 " nucleic acid or its complement under low stringency conditions,

(xxx) "Protocadherin beta 8 " (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8 " nucleic acid or its complement under low stringency conditions,

(xxxi) "REP8 protein " (SEQ ID No:181) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "REP8 protein ", the variant being encoded by a nucleic acid that hybridizes to the "REP8 protein " nucleic acid or its complement under low stringency conditions,

(xxxii) "RING finger protein 5 " (SEQ ID No:182) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RING finger protein 5 ", the variant being encoded by a nucleic acid that hybridizes to the "RING finger protein 5 " nucleic acid or its complement under low stringency conditions,

(xxxiii) "Retinal short-chain dehydrogenase/reductase retSDR2 " (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Retinal short-chain dehydrogenase/reductase retSDR2 ", the variant being encoded by a nucleic acid that hybridizes to the "Retinal short-chain dehydrogenase/reductase retSDR2 " nucleic acid or its complement under low stringency conditions,

(xxxiv) "Stromal cell-derived factor 2-like 1 " (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a

variant of "Stromal cell-derived factor 2-like 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Stromal cell-derived factor 2-like 1 " nucleic acid or its complement under low stringency conditions,

(xxxv) "Thioredoxin domain-containing protein" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions,

(xxxvi) "Voltage-dependent anion channel 1" (SEQ ID No:186) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 1", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the gamma-secretase activity and assembly (trafficking).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:  
expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the bait protein,

and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Nicastrin complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the Nicastrin complex selected from

- (i) "ATP-binding cassette, sub-family A, member 3" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette, sub-family A, member 3", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette, sub-family A, member 3" nucleic acid or its complement under low stringency conditions,
- (ii) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,
- (iii) "ENSG00000144840" (SEQ ID No:167) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENSG00000144840", the variant being encoded by a nucleic acid that hybridizes to the "ENSG00000144840" nucleic acid or its complement under low stringency conditions,
- (iv) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions,
- (v) "FLJ20481" (SEQ ID No:169) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20481", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

- (vi) "FLJ22390" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22390", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22390" nucleic acid or its complement under low stringency conditions,
- (vii) "Hypothetical protein tyrosine phosphatase ensg00000149185 " (SEQ ID No:171) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Hypothetical protein tyrosine phosphatase ensg00000149185 ", the variant being encoded by a nucleic acid that hybridizes to the "Hypothetical protein tyrosine phosphatase ensg00000149185 " nucleic acid or its complement under low stringency conditions,
- (viii) "KIAA1181" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1181", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1181" nucleic acid or its complement under low stringency conditions,
- (ix) "KIAA1533" (SEQ ID No:174) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1533", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1533" nucleic acid or its complement under low stringency conditions,
- (x) "PP1, regulatory subunit 15B " (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP1, regulatory subunit 15B ", the variant being encoded by a nucleic acid that hybridizes to the "PP1, regulatory subunit 15B " nucleic acid or its complement under low stringency conditions,
- (xi) "RING finger protein 5 " (SEQ ID No:182) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RING finger protein 5 ", the variant being encoded by a nucleic acid that hybridizes to the "RING finger protein 5 " nucleic acid or its complement under low stringency conditions, and
- (xii) "Thioredoxin domain-containing protein" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl

(pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising:

- (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
- (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b) or
- (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container:

- (a) the complex of any of No. 1 – 8 and/or the proteins of No. 13 and/or
- (b) an antibody according to No. 17 and/or
- (c) a nucleic acid encoding a protein of the complex of any of No. 1 – 8 and/or a protein of No. 13 and/or
- (d) cells expressing the complex of any of No. 1 – 8 and/or a protein of No. 13 and, optionally,
- (e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for modifying a physiological substrate of the complex comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "ATP-binding cassette, sub-family A, member 3" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette, sub-family A, member 3", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette, sub-family A, member 3" nucleic acid or its complement under low stringency conditions,
- (ii) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant

being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,

(iii) "ENSG00000144840" (SEQ ID No:167) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENSG00000144840", the variant being encoded by a nucleic acid that hybridizes to the "ENSG00000144840" nucleic acid or its complement under low stringency conditions,

(iv) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions,

(v) "FLJ20481" (SEQ ID No:169) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20481", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(vi) "FLJ22390" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22390", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22390" nucleic acid or its complement under low stringency conditions,

(vii) "Hypothetical protein tyrosine phosphatase ensg00000149185 " (SEQ ID No:171) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Hypothetical protein tyrosine phosphatase ensg00000149185 ", the variant being encoded by a nucleic acid that hybridizes to the "Hypothetical protein tyrosine phosphatase ensg00000149185 " nucleic acid or its complement under low stringency conditions,

(viii) "KIAA1181" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1181", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1181" nucleic acid or its complement under low stringency conditions,

(ix) "KIAA1533" (SEQ ID No:174) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1533", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1533" nucleic acid or its complement under low stringency conditions,

(x) "PP1, regulatory subunit 15B " (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"PP1, regulatory subunit 15B ", the variant being encoded by a nucleic acid that hybridizes to the "PP1, regulatory subunit 15B " nucleic acid or its complement under low stringency conditions,

(xi) "RING finger protein 5 " (SEQ ID No:182) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RING finger protein 5 ", the variant being encoded by a nucleic acid that hybridizes to the "RING finger protein 5 " nucleic acid or its complement under low stringency conditions, and/or

(xii) "Thioredoxin domain-containing protein" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to a complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "ATP-binding cassette, sub-family A, member 3" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette, sub-family A, member 3", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette, sub-family A, member 3" nucleic acid or its complement under low stringency conditions,

(ii) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,

(iii) "ENSG00000144840" (SEQ ID No:167) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENSG00000144840", the variant being encoded by a nucleic acid that hybridizes to the "ENSG00000144840" nucleic acid or its complement under low stringency conditions,

- (iv) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions,
- (v) "FLJ20481" (SEQ ID No:169) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20481", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (vi) "FLJ22390" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22390", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22390" nucleic acid or its complement under low stringency conditions,
- (vii) "Hypothetical protein tyrosine phosphatase ensg00000149185 " (SEQ ID No:171) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Hypothetical protein tyrosine phosphatase ensg00000149185 ", the variant being encoded by a nucleic acid that hybridizes to the "Hypothetical protein tyrosine phosphatase ensg00000149185 " nucleic acid or its complement under low stringency conditions,
- (viii) "KIAA1181" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1181", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1181" nucleic acid or its complement under low stringency conditions,
- (ix) "KIAA1533" (SEQ ID No:174) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1533", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1533" nucleic acid or its complement under low stringency conditions,
- (x) "PP1, regulatory subunit 15B " (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP1, regulatory subunit 15B ", the variant being encoded by a nucleic acid that hybridizes to the "PP1, regulatory subunit 15B " nucleic acid or its complement under low stringency conditions,
- (xi) "RING finger protein 5 " (SEQ ID No:182) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RING finger protein 5 ", the variant being encoded by a nucleic acid that hybridizes to the

"RING finger protein 5 " nucleic acid or its complement under low stringency conditions, and/or

(xii) "Thioredoxin domain-containing protein" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, comprising the steps of:

- (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and
- (b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:

- (a) exposing said complex, or a cell or organism containing Nicastrin complex to one or more candidate molecules; and
- (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said

isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether

- (i) "18 kDa microsomal signal peptidase subunit" (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions, and/or
- (iii) "ATP-binding cassette, sub-family A, member 3" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette, sub-family A, member 3", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette, sub-family A, member 3" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions, and/or
- (v) "BACE1" (SEQ ID No:161) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BACE1", the variant being encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "BSCv protein" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BSCv

protein", the variant being encoded by a nucleic acid that hybridizes to the "BSCv protein" nucleic acid or its complement under low stringency conditions, and/or

(vii) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions, and/or

(viii) "Casein kinase II beta chain " (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Casein kinase II beta chain ", the variant being encoded by a nucleic acid that hybridizes to the "Casein kinase II beta chain " nucleic acid or its complement under low stringency conditions, and/or

(ix) "Cathepsin B" (SEQ ID No:165) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cathepsin B", the variant being encoded by a nucleic acid that hybridizes to the "Cathepsin B" nucleic acid or its complement under low stringency conditions, and/or

(x) "Delta-6 fatty acid desaturase " (SEQ ID No:166) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-6 fatty acid desaturase ", the variant being encoded by a nucleic acid that hybridizes to the "Delta-6 fatty acid desaturase " nucleic acid or its complement under low stringency conditions, and/or

(xi) "ENSG00000144840" (SEQ ID No:167) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENSG00000144840", the variant being encoded by a nucleic acid that hybridizes to the "ENSG00000144840" nucleic acid or its complement under low stringency conditions, and/or

(xii) "FLJ13977" (SEQ ID No:168) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13977", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13977" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions, and/or

- (xiv) "FLJ20481" (SEQ ID No:169) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20481", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "FLJ22390" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22390", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22390" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "Hypothetical protein tyrosine phosphatase ensg00000149185 " (SEQ ID No:171) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Hypothetical protein tyrosine phosphatase ensg00000149185 ", the variant being encoded by a nucleic acid that hybridizes to the "Hypothetical protein tyrosine phosphatase ensg00000149185 " nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "ICAM-2" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ICAM-2", the variant being encoded by a nucleic acid that hybridizes to the "ICAM-2" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "KIAA1181" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1181", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1181" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "KIAA1533" (SEQ ID No:174) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1533", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1533" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "Mesenchymal stem cell protein DSCD75 " (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Mesenchymal stem cell protein DSCD75 ", the variant being encoded by a nucleic acid that hybridizes to the "Mesenchymal stem cell protein DSCD75 " nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "NICE-3" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NICE-3", the

variant being encoded by a nucleic acid that hybridizes to the "NICE-3" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the

"Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a

functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin",

the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid

or its complement under low stringency conditions, and/or

(xxiv) "PP1, regulatory subunit 15B " (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"PP1, regulatory subunit 15B ", the variant being encoded by a nucleic acid that

hybridizes to the "PP1, regulatory subunit 15B " nucleic acid or its complement under low stringency conditions, and/or

(xxv) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally

active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being

encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement

under low stringency conditions, and/or

(xxvi) "Presenilin-1" (SEQ ID No:17) or a functionally active derivative thereof, or a

functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin-

1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin-1"

nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "Presenilin-2" (SEQ ID No:152) or a functionally active derivative thereof, or a

functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin-

2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin-2"

nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "Protein amplified in osteosarcoma (OS-9)" (SEQ ID No:178) or a functionally

active derivative thereof, or a functionally active fragment thereof, or a homologue

thereof, or a variant of "Protein amplified in osteosarcoma (OS-9)", the variant being

encoded by a nucleic acid that hybridizes to the "Protein amplified in osteosarcoma (OS-

9)" nucleic acid or its complement under low stringency conditions, and/or

(xxix) "Protein similar to stromal cell-derived factor 2 " (SEQ ID No:179) or a functionally

active derivative thereof, or a functionally active fragment thereof, or a homologue

thereof, or a variant of "Protein similar to stromal cell-derived factor 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to stromal cell-derived factor 2 " nucleic acid or its complement under low stringency conditions, and/or  
 (xxx) "Protocadherin beta 8 " (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8 " nucleic acid or its complement under low stringency conditions, and/or

(xxxi) "REP8 protein " (SEQ ID No:181) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "REP8 protein ", the variant being encoded by a nucleic acid that hybridizes to the "REP8 protein " nucleic acid or its complement under low stringency conditions, and/or

(xxxii) "RING finger protein 5 " (SEQ ID No:182) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RING finger protein 5 ", the variant being encoded by a nucleic acid that hybridizes to the "RING finger protein 5 " nucleic acid or its complement under low stringency conditions, and/or

(xxxiii) "Retinal short-chain dehydrogenase/reductase retSDR2 " (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Retinal short-chain dehydrogenase/reductase retSDR2 ", the variant being encoded by a nucleic acid that hybridizes to the "Retinal short-chain dehydrogenase/reductase retSDR2 " nucleic acid or its complement under low stringency conditions, and/or

(xxxiv) "Stromal cell-derived factor 2-like 1 " (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stromal cell-derived factor 2-like 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Stromal cell-derived factor 2-like 1 " nucleic acid or its complement under low stringency conditions, and/or

(xxxv) "Thioredoxin domain-containing protein" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "Voltage-dependent anion channel 1" (SEQ ID No:186) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 1", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether

- (i) "18 kDa microsomal signal peptidase subunit" (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions, and/or
- (iii) "ATP-binding cassette, sub-family A, member 3" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette, sub-family A, member 3", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette, sub-family A, member 3" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions, and/or

- (v) "BACE1" (SEQ ID No:161) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BACE1", the variant being encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "BSCv protein" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BSCv protein", the variant being encoded by a nucleic acid that hybridizes to the "BSCv protein" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "Casein kinase II beta chain " (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Casein kinase II beta chain ", the variant being encoded by a nucleic acid that hybridizes to the "Casein kinase II beta chain " nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Cathepsin B" (SEQ ID No:165) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cathepsin B", the variant being encoded by a nucleic acid that hybridizes to the "Cathepsin B" nucleic acid or its complement under low stringency conditions, and/or
- (x) "Delta-6 fatty acid desaturase " (SEQ ID No:166) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-6 fatty acid desaturase ", the variant being encoded by a nucleic acid that hybridizes to the "Delta-6 fatty acid desaturase " nucleic acid or its complement under low stringency conditions, and/or
- (xi) "ENSG00000144840" (SEQ ID No:167) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENSG00000144840", the variant being encoded by a nucleic acid that hybridizes to the "ENSG00000144840" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "FLJ13977" (SEQ ID No:168) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13977",

- the variant being encoded by a nucleic acid that hybridizes to the "FLJ13977" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "FLJ20481" (SEQ ID No:169) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20481", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "FLJ22390" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22390", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22390" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "Hypothetical protein tyrosine phosphatase ensg00000149185 " (SEQ ID No:171) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Hypothetical protein tyrosine phosphatase ensg00000149185 ", the variant being encoded by a nucleic acid that hybridizes to the "Hypothetical protein tyrosine phosphatase ensg00000149185 " nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "ICAM-2" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ICAM-2", the variant being encoded by a nucleic acid that hybridizes to the "ICAM-2" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "KIAA1181" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1181", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1181" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "KIAA1533" (SEQ ID No:174) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1533", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1533" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "Mesenchymal stem cell protein DSCD75 " (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a

variant of "Mesenchymal stem cell protein DSCD75 ", the variant being encoded by a nucleic acid that hybridizes to the "Mesenchymal stem cell protein DSCD75 " nucleic acid or its complement under low stringency conditions, and/or

(xxi) "NICE-3" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NICE-3", the variant being encoded by a nucleic acid that hybridizes to the "NICE-3" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "PP1, regulatory subunit 15B " (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP1, regulatory subunit 15B ", the variant being encoded by a nucleic acid that hybridizes to the "PP1, regulatory subunit 15B " nucleic acid or its complement under low stringency conditions, and/or

(xxv) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "Presenilin-1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin-1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin-1" nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "Presenilin-2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin-2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin-2" nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "Protein amplified in osteosarcoma (OS-9)" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue

thereof, or a variant of "Protein amplified in osteosarcoma (OS-9)", the variant being encoded by a nucleic acid that hybridizes to the "Protein amplified in osteosarcoma (OS-9)" nucleic acid or its complement under low stringency conditions, and/or

(xxix) "Protein similar to stromal cell-derived factor 2 " (SEQ ID No:179) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to stromal cell-derived factor 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to stromal cell-derived factor 2 " nucleic acid or its complement under low stringency conditions, and/or

(xxx) "Protocadherin beta 8 " (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8 " nucleic acid or its complement under low stringency conditions, and/or

(xxxi) "REP8 protein " (SEQ ID No:181) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "REP8 protein ", the variant being encoded by a nucleic acid that hybridizes to the "REP8 protein " nucleic acid or its complement under low stringency conditions, and/or

(xxxii) "RING finger protein 5 " (SEQ ID No:182) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RING finger protein 5 ", the variant being encoded by a nucleic acid that hybridizes to the "RING finger protein 5 " nucleic acid or its complement under low stringency conditions, and/or

(xxxiii) "Retinal short-chain dehydrogenase/reductase retSDR2 " (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Retinal short-chain dehydrogenase/reductase retSDR2 ", the variant being encoded by a nucleic acid that hybridizes to the "Retinal short-chain dehydrogenase/reductase retSDR2 " nucleic acid or its complement under low stringency conditions, and/or

(xxxiv) "Stromal cell-derived factor 2-like 1 " (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stromal cell-derived factor 2-like 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Stromal cell-derived factor 2-like 1 " nucleic acid or its complement under low stringency conditions, and/or

(xxxv) "Thioredoxin domain-containing protein" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "Voltage-dependent anion channel 1" (SEQ ID No:186) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 1", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the gamma-secretase activity and assembly (trafficking) of, or protein composition of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins:

(i) "18 kDa microsomal signal peptidase subunit" (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit", the variant being encoded by a

nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit" nucleic acid or its complement under low stringency conditions,

(ii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(iii) "ATP-binding cassette, sub-family A, member 3" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ATP-binding cassette, sub-family A, member 3", the variant being encoded by a nucleic acid that hybridizes to the "ATP-binding cassette, sub-family A, member 3" nucleic acid or its complement under low stringency conditions,

(iv) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,

(v) "BACE1" (SEQ ID No:161) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BACE1", the variant being encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,

(vi) "BSCv protein" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BSCv protein", the variant being encoded by a nucleic acid that hybridizes to the "BSCv protein" nucleic acid or its complement under low stringency conditions,

(vii) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,

(viii) "Casein kinase II beta chain " (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Casein kinase II beta chain ", the variant being encoded by a nucleic acid that hybridizes to the "Casein kinase II beta chain " nucleic acid or its complement under low stringency conditions,

- (ix) "Cathepsin B" (SEQ ID No:165) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cathepsin B", the variant being encoded by a nucleic acid that hybridizes to the "Cathepsin B" nucleic acid or its complement under low stringency conditions,
- (x) "Delta-6 fatty acid desaturase " (SEQ ID No:166) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-6 fatty acid desaturase ", the variant being encoded by a nucleic acid that hybridizes to the "Delta-6 fatty acid desaturase " nucleic acid or its complement under low stringency conditions,
- (xi) "ENSG00000144840" (SEQ ID No:167) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ENSG00000144840", the variant being encoded by a nucleic acid that hybridizes to the "ENSG00000144840" nucleic acid or its complement under low stringency conditions,
- (xii) "FLJ13977" (SEQ ID No:168) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13977", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13977" nucleic acid or its complement under low stringency conditions,
- (xiii) "FLJ20342" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20342", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20342" nucleic acid or its complement under low stringency conditions,
- (xiv) "FLJ20481" (SEQ ID No:169) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ20481", the variant being encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xv) "FLJ22390" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ22390", the variant being encoded by a nucleic acid that hybridizes to the "FLJ22390" nucleic acid or its complement under low stringency conditions,
- (xvi) "Hypothetical protein tyrosine phosphatase ensg00000149185 " (SEQ ID No:171) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Hypothetical protein tyrosine phosphatase ensg00000149185 ", the variant being encoded by a nucleic acid that hybridizes to the

"Hypothetical protein tyrosine phosphatase ensg00000149185 " nucleic acid or its complement under low stringency conditions,

(xvii) "ICAM-2" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ICAM-2", the variant being encoded by a nucleic acid that hybridizes to the "ICAM-2" nucleic acid or its complement under low stringency conditions,

(xviii) "KIAA1181" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1181", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1181" nucleic acid or its complement under low stringency conditions,

(xix) "KIAA1533" (SEQ ID No:174) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1533", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1533" nucleic acid or its complement under low stringency conditions,

(xx) "Mesenchymal stem cell protein DSCD75 " (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Mesenchymal stem cell protein DSCD75 ", the variant being encoded by a nucleic acid that hybridizes to the "Mesenchymal stem cell protein DSCD75 " nucleic acid or its complement under low stringency conditions,

(xxi) "NICE-3" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NICE-3", the variant being encoded by a nucleic acid that hybridizes to the "NICE-3" nucleic acid or its complement under low stringency conditions,

(xxii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xxiii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(xxiv) "PP1, regulatory subunit 15B " (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP1, regulatory subunit 15B ", the variant being encoded by a nucleic acid that

hybridizes to the "PP1, regulatory subunit 15B " nucleic acid or its complement under low stringency conditions,

(xxv) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,

(xxvi) "Presenilin-1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin-1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin-1" nucleic acid or its complement under low stringency conditions,

(xxvii) "Presenilin-2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin-2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin-2" nucleic acid or its complement under low stringency conditions,

(xxviii) "Protein amplified in osteosarcoma (OS-9)" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein amplified in osteosarcoma (OS-9)", the variant being encoded by a nucleic acid that hybridizes to the "Protein amplified in osteosarcoma (OS-9)" nucleic acid or its complement under low stringency conditions,

(xxix) "Protein similar to stromal cell-derived factor 2 " (SEQ ID No:179) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein similar to stromal cell-derived factor 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Protein similar to stromal cell-derived factor 2 " nucleic acid or its complement under low stringency conditions,

(xxx) "Protocadherin beta 8 " (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8 " nucleic acid or its complement under low stringency conditions,

(xxxi) "REP8 protein " (SEQ ID No:181) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "REP8 protein ", the variant being encoded by a nucleic acid that hybridizes to the "REP8 protein " nucleic acid or its complement under low stringency conditions,

(xxxii) "RING finger protein 5 " (SEQ ID No:182) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RING finger protein 5 ", the variant being encoded by a nucleic acid that hybridizes to the "RING finger protein 5 " nucleic acid or its complement under low stringency conditions,

(xxxiii) "Retinal short-chain dehydrogenase/reductase retSDR2 " (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Retinal short-chain dehydrogenase/reductase retSDR2 ", the variant being encoded by a nucleic acid that hybridizes to the "Retinal short-chain dehydrogenase/reductase retSDR2 " nucleic acid or its complement under low stringency conditions,

(xxxiv) "Stromal cell-derived factor 2-like 1 " (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stromal cell-derived factor 2-like 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Stromal cell-derived factor 2-like 1 " nucleic acid or its complement under low stringency conditions,

(xxxv) "Thioredoxin domain-containing protein" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, and/or (xxxvi) "Voltage-dependent anion channel 1" (SEQ ID No:186) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 1", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

The invention further relates to the Aph-1a complex:

1. A protein complex selected from complex (I) and comprising

(a) at least one first protein selected from the group consisting of:

- (i) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (ii) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,
- (iii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iv) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,
- (v) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and
- (vi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

- (i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,
- (ii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue

- thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,
- (iii) "Brain-specific GTP-binding protein " (SEQ ID No:187) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Brain-specific GTP-binding protein ", the variant being encoded by a nucleic acid that hybridizes to the "Brain-specific GTP-binding protein " nucleic acid or its complement under low stringency conditions,
- (iv) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,
- (v) "Cerebral protein-10 " (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein-10", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein-10 " nucleic acid or its complement under low stringency conditions,
- (vi) "Dihydrofolate reductase " (SEQ ID No:188) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dihydrofolate reductase ", the variant being encoded by a nucleic acid that hybridizes to the "Dihydrofolate reductase " nucleic acid or its complement under low stringency conditions,
- (vii) "Endocytic receptor Endo180" (SEQ ID No:189) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Endocytic receptor Endo180", the variant being encoded by a nucleic acid that hybridizes to the "Endocytic receptor Endo180" nucleic acid or its complement under low stringency conditions,
- (viii) "FLJ13660" (SEQ ID No:190) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13660", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13660" nucleic acid or its complement under low stringency conditions,
- (ix) "HU-K4" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4" nucleic acid or its complement under low stringency conditions,

- (x) "Integral membrane protein 2B (ITM2B) " (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B) ", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B) " nucleic acid or its complement under low stringency conditions,
- (xi) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions,
- (xii) "KIAA0251" (SEQ ID No:191) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0251", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0251" nucleic acid or its complement under low stringency conditions,
- (xiii) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xiv) "KIAA0971" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0971", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0971" nucleic acid or its complement under low stringency conditions,
- (xv) "KIAA1250" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1250", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions,
- (xvi) "Mesenchymal stem cell protein DSCD75" (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Mesenchymal stem cell protein DSCD75", the variant being encoded by a nucleic acid that hybridizes to the "Mesenchymal stem cell protein DSCD75" nucleic acid or its complement under low stringency conditions,
- (xvii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xviii) "PP2C gamma" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP2C gamma", the variant being encoded by a nucleic acid that hybridizes to the "PP2C gamma" nucleic acid or its complement under low stringency conditions,

(xix) "Protocadherin 7 " (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin 7 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin 7 " nucleic acid or its complement under low stringency conditions,

(xx) "Protocadherin beta 16 " (SEQ ID No:197) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 16 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 16 " nucleic acid or its complement under low stringency conditions,

(xxi) "Protocadherin beta 8 " (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8 " nucleic acid or its complement under low stringency conditions,

(xxii) "RAB-18" (SEQ ID No:198) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RAB-18", the variant being encoded by a nucleic acid that hybridizes to the "RAB-18" nucleic acid or its complement under low stringency conditions,

(xxiii) "Rab3 GTPase-activating protein, non-catalytic subunit " (SEQ ID No:199) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Rab3 GTPase-activating protein, non-catalytic subunit ", the variant being encoded by a nucleic acid that hybridizes to the "Rab3 GTPase-activating protein, non-catalytic subunit " nucleic acid or its complement under low stringency conditions,

(xxiv) "Retinal short-chain dehydrogenase/reductase retSDR2" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Retinal short-chain dehydrogenase/reductase retSDR2", the variant being encoded by a nucleic acid that hybridizes to the "Retinal short-chain dehydrogenase/reductase retSDR2" nucleic acid or its complement under low stringency conditions,

(xxv) "SMAP-1B" (SEQ ID No:200) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SMAP-1B", the variant being encoded by a nucleic acid that hybridizes to the "SMAP-1B" nucleic acid or its complement under low stringency conditions,

(xxvi) "Sideroflexin 1" (SEQ ID No:201) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sideroflexin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sideroflexin 1" nucleic acid or its complement under low stringency conditions,

(xxvii) "Signal transducer and activator of transcription-1 " (SEQ ID No:202) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Signal transducer and activator of transcription-1 ", the variant being encoded by a nucleic acid that hybridizes to the "Signal transducer and activator of transcription-1 " nucleic acid or its complement under low stringency conditions,

(xxviii) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions,

(xxix) "Sterol O-acyltransferase 1 " (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterol O-acyltransferase 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Sterol O-acyltransferase 1 " nucleic acid or its complement under low stringency conditions,

(xxx) "Thioredoxin domain-containing protein " (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein ", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein " nucleic acid or its complement under low stringency conditions,

(xxxi) "Triple functional domain protein (PTPRF interacting) " (SEQ ID No:204) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Triple functional domain protein (PTPRF interacting) ", the variant being encoded by a nucleic acid that hybridizes to the "Triple functional

domain protein (PTPRF interacting) " nucleic acid or its complement under low stringency conditions, and

(xxxii) "Vacuolar ATP synthase membrane sector associated protein m8-9 " (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Vacuolar ATP synthase membrane sector associated protein m8-9 ", the variant being encoded by a nucleic acid that hybridizes to the "Vacuolar ATP synthase membrane sector associated protein m8-9 " nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. The protein complex according to No. 1 wherein the first protein is the protein "Aph-1a" (SEQ ID No:2), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid under low stringency conditions.

3. The protein complex according to No. 1 comprising the following proteins:

- (i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,
- (ii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

- (iii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,
- (v) "Brain-specific GTP-binding protein " (SEQ ID No:187) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Brain-specific GTP-binding protein ", the variant being encoded by a nucleic acid that hybridizes to the "Brain-specific GTP-binding protein " nucleic acid or its complement under low stringency conditions,
- (vi) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,
- (vii) "Cerebral protein-10 " (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein-10 ", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein-10 " nucleic acid or its complement under low stringency conditions,
- (viii) "Dihydrofolate reductase " (SEQ ID No:188) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dihydrofolate reductase ", the variant being encoded by a nucleic acid that hybridizes to the "Dihydrofolate reductase " nucleic acid or its complement under low stringency conditions,
- (ix) "Endocytic receptor Endo180" (SEQ ID No:189) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Endocytic receptor Endo180", the variant being encoded by a nucleic acid that hybridizes to the "Endocytic receptor Endo180" nucleic acid or its complement under low stringency conditions,
- (x) "FLJ13660" (SEQ ID No:190) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13660",

the variant being encoded by a nucleic acid that hybridizes to the "FLJ13660" nucleic acid or its complement under low stringency conditions,

(xi) "HU-K4" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4" nucleic acid or its complement under low stringency conditions,

(xii) "Integral membrane protein 2B (ITM2B) " (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B) ", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B) " nucleic acid or its complement under low stringency conditions,

(xiii) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions,

(xiv) "KIAA0251" (SEQ ID No:191) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0251", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0251" nucleic acid or its complement under low stringency conditions,

(xv) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,

(xvi) "KIAA0971" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0971", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0971" nucleic acid or its complement under low stringency conditions,

(xvii) "KIAA1250" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1250", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions,

(xviii) "Mesenchymal stem cell protein DSCD75" (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Mesenchymal stem cell protein DSCD75", the variant being encoded by a

nucleic acid that hybridizes to the "Mesenchymal stem cell protein DSCD75" nucleic acid or its complement under low stringency conditions,

(xix) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xx) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(xxi) "PP2C gamma" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP2C gamma", the variant being encoded by a nucleic acid that hybridizes to the "PP2C gamma" nucleic acid or its complement under low stringency conditions,

(xxii) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,

(xxiii) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,

(xxiv) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions,

(xxv) "Protocadherin 7 " (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin 7.", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin 7 " nucleic acid or its complement under low stringency conditions,

(xxvi) "Protocadherin beta 16 " (SEQ ID No:197) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 16 ", the variant being encoded by a nucleic acid that hybridizes to

the "Protocadherin beta 16 " nucleic acid or its complement under low stringency conditions,

(xxvii) "Protocadherin beta 8 " (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8 " nucleic acid or its complement under low stringency conditions,

(xxviii) "RAB-18" (SEQ ID No:198) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RAB-18", the variant being encoded by a nucleic acid that hybridizes to the "RAB-18" nucleic acid or its complement under low stringency conditions,

(xxix) "Rab3 GTPase-activating protein, non-catalytic subunit " (SEQ ID No:199) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Rab3 GTPase-activating protein, non-catalytic subunit ", the variant being encoded by a nucleic acid that hybridizes to the "Rab3 GTPase-activating protein, non-catalytic subunit " nucleic acid or its complement under low stringency conditions,

(xxx) "Retinal short-chain dehydrogenase/reductase retSDR2" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Retinal short-chain dehydrogenase/reductase retSDR2", the variant being encoded by a nucleic acid that hybridizes to the "Retinal short-chain dehydrogenase/reductase retSDR2" nucleic acid or its complement under low stringency conditions,

(xxxi) "SMAP-1B" (SEQ ID No:200) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SMAP-1B", the variant being encoded by a nucleic acid that hybridizes to the "SMAP-1B" nucleic acid or its complement under low stringency conditions,

(xxxii) "Sideroflexin 1" (SEQ ID No:201) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sideroflexin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sideroflexin 1" nucleic acid or its complement under low stringency conditions,

(xxxiii) "Signal transducer and activator of transcription-1 " (SEQ ID No:202) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Signal transducer and activator of transcription-1 ",

the variant being encoded by a nucleic acid that hybridizes to the "Signal transducer and activator of transcription-1 " nucleic acid or its complement under low stringency conditions,

(xxxiv) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions,

(xxxv) "Sterol O-acyltransferase 1 " (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterol O-acyltransferase 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Sterol O-acyltransferase 1 " nucleic acid or its complement under low stringency conditions,

(xxxvi) "Thioredoxin domain-containing protein " (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein ", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein " nucleic acid or its complement under low stringency conditions,

(xxxvii) "Triple functional domain protein (PTPRF interacting) " (SEQ ID No:204) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Triple functional domain protein (PTPRF interacting) ", the variant being encoded by a nucleic acid that hybridizes to the "Triple functional domain protein (PTPRF interacting) " nucleic acid or its complement under low stringency conditions, and/or

(xxxviii) "Vacuolar ATP synthase membrane sector associated protein m8-9 " (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Vacuolar ATP synthase membrane sector associated protein m8-9 ", the variant being encoded by a nucleic acid that hybridizes to the "Vacuolar ATP synthase membrane sector associated protein m8-9 " nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising at least 7 but no more than 37 of the following proteins:

- (i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,
- (ii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,
- (iii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,
- (v) "Brain-specific GTP-binding protein " (SEQ ID No:187) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Brain-specific GTP-binding protein ", the variant being encoded by a nucleic acid that hybridizes to the "Brain-specific GTP-binding protein " nucleic acid or its complement under low stringency conditions,
- (vi) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,
- (vii) "Cerebral protein-10 " (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein-10 ", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein-10 " nucleic acid or its complement under low stringency conditions,
- (viii) "Dihydrofolate reductase " (SEQ ID No:188) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dihydrofolate reductase ", the variant being encoded by a nucleic acid that hybridizes to

the "Dihydrofolate reductase " nucleic acid or its complement under low stringency conditions,

(ix) "Endocytic receptor Endo180" (SEQ ID No:189) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Endocytic receptor Endo180", the variant being encoded by a nucleic acid that hybridizes to the "Endocytic receptor Endo180" nucleic acid or its complement under low stringency conditions,

(x) "FLJ13660" (SEQ ID No:190) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13660", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13660" nucleic acid or its complement under low stringency conditions,

(xi) "HU-K4" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4" nucleic acid or its complement under low stringency conditions,

(xii) "Integral membrane protein 2B (ITM2B) " (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B) ", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B) " nucleic acid or its complement under low stringency conditions,

(xiii) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions,

(xiv) "KIAA0251" (SEQ ID No:191) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0251", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0251" nucleic acid or its complement under low stringency conditions,

(xv) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,

(xvi) "KIAA0971" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0971",

- the variant being encoded by a nucleic acid that hybridizes to the "KIAA0971" nucleic acid or its complement under low stringency conditions,
- (xvii) "KIAA1250" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1250", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions,
- (xviii) "Mesenchymal stem cell protein DSCD75" (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Mesenchymal stem cell protein DSCD75", the variant being encoded by a nucleic acid that hybridizes to the "Mesenchymal stem cell protein DSCD75" nucleic acid or its complement under low stringency conditions,
- (xix) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xx) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (xxi) "PP2C gamma" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP2C gamma", the variant being encoded by a nucleic acid that hybridizes to the "PP2C gamma" nucleic acid or its complement under low stringency conditions,
- (xxii) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,
- (xxiii) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,
- (xxiv) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin

2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions,

(xxv) "Protocadherin 7 " (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Protocadherin 7 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin 7 " nucleic acid or its complement under low stringency conditions,

(xxvi) "Protocadherin beta 16 " (SEQ ID No:197) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 16 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 16 " nucleic acid or its complement under low stringency conditions,

(xxvii) "Protocadherin beta 8 " (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8 " nucleic acid or its complement under low stringency conditions,

(xxviii) "RAB-18" (SEQ ID No:198) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RAB-18", the variant being encoded by a nucleic acid that hybridizes to the "RAB-18" nucleic acid or its complement under low stringency conditions,

(xxix) "Rab3 GTPase-activating protein, non-catalytic subunit " (SEQ ID No:199) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Rab3 GTPase-activating protein, non-catalytic subunit ", the variant being encoded by a nucleic acid that hybridizes to the "Rab3 GTPase-activating protein, non-catalytic subunit " nucleic acid or its complement under low stringency conditions,

(xxx) "Retinal short-chain dehydrogenase/reductase retSDR2" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Retinal short-chain dehydrogenase/reductase retSDR2", the variant being encoded by a nucleic acid that hybridizes to the "Retinal short-chain dehydrogenase/reductase retSDR2" nucleic acid or its complement under low stringency conditions,

(xxxi) "SMAP-1B" (SEQ ID No:200) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SMAP-1B",

the variant being encoded by a nucleic acid that hybridizes to the "SMAP-1B" nucleic acid or its complement under low stringency conditions,

(xxxii) "Sideroflexin 1" (SEQ ID No:201) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sideroflexin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sideroflexin 1" nucleic acid or its complement under low stringency conditions,

(xxxiii) "Signal transducer and activator of transcription-1 " (SEQ ID No:202) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Signal transducer and activator of transcription-1 ", the variant being encoded by a nucleic acid that hybridizes to the "Signal transducer and activator of transcription-1 " nucleic acid or its complement under low stringency conditions,

(xxxiv) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions,

(xxxv) "Sterol O-acyltransferase 1 " (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterol O-acyltransferase 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Sterol O-acyltransferase 1 " nucleic acid or its complement under low stringency conditions,

(xxxvi) "Thioredoxin domain-containing protein " (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein ", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein " nucleic acid or its complement under low stringency conditions,

(xxxvii) "Triple functional domain protein (PTPRF interacting) " (SEQ ID No:204) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Triple functional domain protein (PTPRF interacting) ", the variant being encoded by a nucleic acid that hybridizes to the "Triple functional domain protein (PTPRF interacting) " nucleic acid or its complement under low stringency conditions,

(xxxviii) "Vacuolar ATP synthase membrane sector associated protein m8-9 " (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Vacuolar ATP synthase membrane sector associated protein m8-9 ", the variant being encoded by a nucleic acid that hybridizes to the "Vacuolar ATP synthase membrane sector associated protein m8-9 " nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the gamma-secretase activity and assembly (trafficking)

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:  
expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Aph-1a complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the Aph-1a complex selected from

(i) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,

(ii) "Cerebral protein-10 " (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein-10 ", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein-10 " nucleic acid or its complement under low stringency conditions,

(iii) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions,

(iv) "KIAA0251" (SEQ ID No:191) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0251", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0251" nucleic acid or its complement under low stringency conditions,

(v) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,

(vi) "KIAA0971" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0971", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0971" nucleic acid or its complement under low stringency conditions,

(vii) "KIAA1250" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1250",

the variant being encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions,

(viii) "Mesenchymal stem cell protein DSCD75" (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Mesenchymal stem cell protein DSCD75", the variant being encoded by a nucleic acid that hybridizes to the "Mesenchymal stem cell protein DSCD75" nucleic acid or its complement under low stringency conditions,

(ix) "Protocadherin 7 " (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin 7 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin 7 " nucleic acid or its complement under low stringency conditions,

(x) "Protocadherin beta 16 " (SEQ ID No:197) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 16 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 16 " nucleic acid or its complement under low stringency conditions,

(xi) "Protocadherin beta 8 " (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8 " nucleic acid or its complement under low stringency conditions,

(xii) "Retinal short-chain dehydrogenase/reductase retSDR2" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Retinal short-chain dehydrogenase/reductase retSDR2", the variant being encoded by a nucleic acid that hybridizes to the "Retinal short-chain dehydrogenase/reductase retSDR2" nucleic acid or its complement under low stringency conditions,

(xiii) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions,

(xiv) "Thioredoxin domain-containing protein " (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a

variant of "Thioredoxin domain-containing protein ", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein " nucleic acid or its complement under low stringency conditions, and

(xv) "Vacuolar ATP synthase membrane sector associated protein m8-9 " (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Vacuolar ATP synthase membrane sector associated protein m8-9 ", the variant being encoded by a nucleic acid that hybridizes to the "Vacuolar ATP synthase membrane sector associated protein m8-9 " nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising:

(a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or

(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b) or

(c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least one nucleic

acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container:

- (a) the complex of any of No. 1 - 8 and/or the proteins of No. 13 and/or
- (b) an antibody according to No. 17 and/or
- (c) a nucleic acid encoding a protein of the complex of any of No. 1 - 8 and/or a protein of No. 13 and/or
- (d) cells expressing the complex of any of No. 1 - 8 and/or a protein of No. 13 and, optionally,
- (e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for modifying a physiological substrate of the complex comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,
- (ii) "Cerebral protein-10 " (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein-10 ", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein-10 " nucleic acid or its complement under low stringency conditions,
- (iii) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions,
- (iv) "KIAA0251" (SEQ ID No:191) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0251", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0251" nucleic acid or its complement under low stringency conditions,
- (v) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (vi) "KIAA0971" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0971", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0971" nucleic acid or its complement under low stringency conditions,
- (vii) "KIAA1250" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1250", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions,
- (viii) "Mesenchymal stem cell protein DSCD75" (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Mesenchymal stem cell protein DSCD75", the variant being encoded by a

nucleic acid that hybridizes to the "Mesenchymal stem cell protein DSCD75" nucleic acid or its complement under low stringency conditions,

(ix) "Protocadherin 7 " (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Protocadherin 7 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin 7 " nucleic acid or its complement under low stringency conditions,

(x) "Protocadherin beta 16 " (SEQ ID No:197) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Protocadherin beta 16 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 16 " nucleic acid or its complement under low stringency conditions,

(xi) "Protocadherin beta 8 " (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Protocadherin beta 8 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8 " nucleic acid or its complement under low stringency conditions,

(xii) "Retinal short-chain dehydrogenase/reductase retSDR2" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Retinal short-chain dehydrogenase/reductase retSDR2", the variant being encoded by a nucleic acid that hybridizes to the "Retinal short-chain dehydrogenase/reductase retSDR2" nucleic acid or its complement under low stringency conditions,

(xiii) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions,

(xiv) "Thioredoxin domain-containing protein " (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein ", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein " nucleic acid or its complement under low stringency conditions, and/or

(xv) "Vacuolar ATP synthase membrane sector associated protein m8-9 " (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment

thereof, or a homologue thereof, or a variant of "Vacuolar ATP synthase membrane sector associated protein m8-9 ", the variant being encoded by a nucleic acid that hybridizes to the "Vacuolar ATP synthase membrane sector associated protein m8-9 " nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to a complex of anyone of No. 1 - 8 and/or any of the following the proteins:

- (i) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,
- (ii) "Cerebral protein-10 " (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein-10 ", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein-10 " nucleic acid or its complement under low stringency conditions,
- (iii) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions,
- (iv) "KIAA0251" (SEQ ID No:191) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0251", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0251" nucleic acid or its complement under low stringency conditions,
- (v) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (vi) "KIAA0971" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0971",

the variant being encoded by a nucleic acid that hybridizes to the "KIAA0971" nucleic acid or its complement under low stringency conditions,

(vii) "KIAA1250" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1250", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions,

(viii) "Mesenchymal stem cell protein DSCD75" (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Mesenchymal stem cell protein DSCD75", the variant being encoded by a nucleic acid that hybridizes to the "Mesenchymal stem cell protein DSCD75" nucleic acid or its complement under low stringency conditions,

(ix) "Protocadherin 7 " (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin 7 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin 7 " nucleic acid or its complement under low stringency conditions,

(x) "Protocadherin beta 16 " (SEQ ID No:197) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 16 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 16 " nucleic acid or its complement under low stringency conditions,

(xi) "Protocadherin beta 8 " (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8 " nucleic acid or its complement under low stringency conditions,

(xii) "Retinal short-chain dehydrogenase/reductase retSDR2" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Retinal short-chain dehydrogenase/reductase retSDR2", the variant being encoded by a nucleic acid that hybridizes to the "Retinal short-chain dehydrogenase/reductase retSDR2" nucleic acid or its complement under low stringency conditions,

(xiii) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being

encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions,

(xiv) "Thioredoxin domain-containing protein " (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein ", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein " nucleic acid or its complement under low stringency conditions, and/or

(xv) "Vacuolar ATP synthase membrane sector associated protein m8-9 " (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Vacuolar ATP synthase membrane sector associated protein m8-9 ", the variant being encoded by a nucleic acid that hybridizes to the "Vacuolar ATP synthase membrane sector associated protein m8-9 " nucleic acid or its complement under low stringency conditions, comprising the steps of:

(a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:

(a) exposing said complex, or a cell or organism containing Aph-1a complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether

- (i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions, and/or
- (ii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions, and/or
- (iii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions, and/or
- (v) "Brain-specific GTP-binding protein " (SEQ ID No:187) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a

variant of "Brain-specific GTP-binding protein ", the variant being encoded by a nucleic acid that hybridizes to the "Brain-specific GTP-binding protein " nucleic acid or its complement under low stringency conditions, and/or

(vi) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions, and/or

(vii) "Cerebral protein-10 " (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein-10 ", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein-10 " nucleic acid or its complement under low stringency conditions, and/or

(viii) "Dihydrofolate reductase " (SEQ ID No:188) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dihydrofolate reductase ", the variant being encoded by a nucleic acid that hybridizes to the "Dihydrofolate reductase " nucleic acid or its complement under low stringency conditions, and/or

(ix) "Endocytic receptor Endo180" (SEQ ID No:189) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Endocytic receptor Endo180", the variant being encoded by a nucleic acid that hybridizes to the "Endocytic receptor Endo180" nucleic acid or its complement under low stringency conditions, and/or

(x) "FLJ13660" (SEQ ID No:190) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13660", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13660" nucleic acid or its complement under low stringency conditions, and/or

(xi) "HU-K4" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4" nucleic acid or its complement under low stringency conditions, and/or

(xii) "Integral membrane protein 2B (ITM2B) " (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B) ", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B) " nucleic acid or its complement under low stringency conditions, and/or

- (xiii) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "KIAA0251" (SEQ ID No:191) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0251", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0251" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "KIAA0971" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0971", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0971" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "KIAA1250" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1250", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "Mesenchymal stem cell protein DSCD75" (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Mesenchymal stem cell protein DSCD75", the variant being encoded by a nucleic acid that hybridizes to the "Mesenchymal stem cell protein DSCD75" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

- (xxi) "PP2C gamma" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP2C gamma", the variant being encoded by a nucleic acid that hybridizes to the "PP2C gamma" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions, and/or
- (xxiii) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and/or
- (xxiv) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions, and/or
- (xxv) "Protocadherin 7 " (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin 7 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin 7 " nucleic acid or its complement under low stringency conditions, and/or
- (xxvi) "Protocadherin beta 16 " (SEQ ID No:197) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 16 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 16 " nucleic acid or its complement under low stringency conditions, and/or
- (xxvii) "Protocadherin beta 8 " (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8 " nucleic acid or its complement under low stringency conditions, and/or
- (xxviii) "RAB-18" (SEQ ID No:198) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RAB-18", the variant being encoded by a nucleic acid that hybridizes to the "RAB-18" nucleic acid or its complement under low stringency conditions, and/or

(xxix) "Rab3 GTPase-activating protein, non-catalytic subunit " (SEQ ID No:199) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Rab3 GTPase-activating protein, non-catalytic subunit ", the variant being encoded by a nucleic acid that hybridizes to the "Rab3 GTPase-activating protein, non-catalytic subunit " nucleic acid or its complement under low stringency conditions, and/or

(xxx) "Retinal short-chain dehydrogenase/reductase retSDR2" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Retinal short-chain dehydrogenase/reductase retSDR2", the variant being encoded by a nucleic acid that hybridizes to the "Retinal short-chain dehydrogenase/reductase retSDR2" nucleic acid or its complement under low stringency conditions, and/or

(xxxi) "SMAP-1B" (SEQ ID No:200) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SMAP-1B", the variant being encoded by a nucleic acid that hybridizes to the "SMAP-1B" nucleic acid or its complement under low stringency conditions, and/or

(xxxii) "Sideroflexin 1" (SEQ ID No:201) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sideroflexin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sideroflexin 1" nucleic acid or its complement under low stringency conditions, and/or

(xxxiii) "Signal transducer and activator of transcription-1 " (SEQ ID No:202) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Signal transducer and activator of transcription-1 ", the variant being encoded by a nucleic acid that hybridizes to the "Signal transducer and activator of transcription-1 " nucleic acid or its complement under low stringency conditions, and/or

(xxxiv) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions, and/or

(xxxv) "Sterol O-acyltransferase 1 " (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterol O-acyltransferase 1 ", the variant being encoded by a nucleic acid that hybridizes

to the "Sterol O-acyltransferase 1 " nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "Thioredoxin domain-containing protein " (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein ", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein " nucleic acid or its complement under low stringency conditions, and/or

(xxxvii) "Triple functional domain protein (PTPRF interacting) " (SEQ ID No:204) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Triple functional domain protein (PTPRF interacting) ", the variant being encoded by a nucleic acid that hybridizes to the "Triple functional domain protein (PTPRF interacting) " nucleic acid or its complement under low stringency conditions, and/or

(xxxviii) "Vacuolar ATP synthase membrane sector associated protein m8-9 " (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Vacuolar ATP synthase membrane sector associated protein m8-9 ", the variant being encoded by a nucleic acid that hybridizes to the "Vacuolar ATP synthase membrane sector associated protein m8-9 " nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether (i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions, and/or

- (ii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions, and/or
- (iii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions, and/or
- (v) "Brain-specific GTP-binding protein " (SEQ ID No:187) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Brain-specific GTP-binding protein ", the variant being encoded by a nucleic acid that hybridizes to the "Brain-specific GTP-binding protein " nucleic acid or its complement under low stringency conditions, and/or
- (vi) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "Cerebral protein-10 " (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein-10 ", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein-10 " nucleic acid or its complement under low stringency conditions, and/or
- (viii) "Dihydrofolate reductase " (SEQ ID No:188) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dihydrofolate reductase ", the variant being encoded by a nucleic acid that hybridizes to the "Dihydrofolate reductase " nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Endocytic receptor Endo180" (SEQ ID No:189) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Endocytic receptor Endo180", the variant being encoded by a nucleic acid that

hybridizes to the "Endocytic receptor Endo180" nucleic acid or its complement under low stringency conditions, and/or

(x) "FLJ13660" (SEQ ID No:190) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13660", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13660" nucleic acid or its complement under low stringency conditions, and/or

(xi) "HU-K4" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4" nucleic acid or its complement under low stringency conditions, and/or

(xii) "Integral membrane protein 2B (ITM2B) " (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B) ", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B) " nucleic acid or its complement under low stringency conditions, and/or

(xiii) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "KIAA0251" (SEQ ID No:191) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0251", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0251" nucleic acid or its complement under low stringency conditions, and/or

(xv) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "KIAA0971" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0971", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0971" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "KIAA1250" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1250",

the variant being encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "Mesenchymal stem cell protein DSCD75" (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Mesenchymal stem cell protein DSCD75", the variant being encoded by a nucleic acid that hybridizes to the "Mesenchymal stem cell protein DSCD75" nucleic acid or its complement under low stringency conditions, and/or

(xix) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(xx) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "PP2C gamma" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP2C gamma", the variant being encoded by a nucleic acid that hybridizes to the "PP2C gamma" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "Protocadherin 7" (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Protocadherin 7 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin 7 " nucleic acid or its complement under low stringency conditions, and/or (xxvi) "Protocadherin beta 16 " (SEQ ID No:197) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 16 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 16 " nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "Protocadherin beta 8 " (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8 " nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "RAB-18" (SEQ ID No:198) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RAB-18", the variant being encoded by a nucleic acid that hybridizes to the "RAB-18" nucleic acid or its complement under low stringency conditions, and/or

(xxix) "Rab3 GTPase-activating protein, non-catalytic subunit " (SEQ ID No:199) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Rab3 GTPase-activating protein, non-catalytic subunit ", the variant being encoded by a nucleic acid that hybridizes to the "Rab3 GTPase-activating protein, non-catalytic subunit " nucleic acid or its complement under low stringency conditions, and/or

(xxx) "Retinal short-chain dehydrogenase/reductase retSDR2" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Retinal short-chain dehydrogenase/reductase retSDR2", the variant being encoded by a nucleic acid that hybridizes to the "Retinal short-chain dehydrogenase/reductase retSDR2" nucleic acid or its complement under low stringency conditions, and/or

(xxxi) "SMAP-1B" (SEQ ID No:200) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SMAP-1B", the variant being encoded by a nucleic acid that hybridizes to the "SMAP-1B" nucleic acid or its complement under low stringency conditions, and/or

(xxxii) "Sideroflexin 1" (SEQ ID No:201) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sideroflexin

1", the variant being encoded by a nucleic acid that hybridizes to the "Sideroflexin 1" nucleic acid or its complement under low stringency conditions, and/or

(xxxiii) "Signal transducer and activator of transcription-1 " (SEQ ID No:202) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Signal transducer and activator of transcription-1 ", the variant being encoded by a nucleic acid that hybridizes to the "Signal transducer and activator of transcription-1 " nucleic acid or its complement under low stringency conditions, and/or

(xxxiv) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions, and/or

(xxxv) "Sterol O-acyltransferase 1 " (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterol O-acyltransferase 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Sterol O-acyltransferase 1 " nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "Thioredoxin domain-containing protein " (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein ", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein " nucleic acid or its complement under low stringency conditions, and/or

(xxxvii) "Triple functional domain protein (PTPRF interacting) " (SEQ ID No:204) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Triple functional domain protein (PTPRF interacting) ", the variant being encoded by a nucleic acid that hybridizes to the "Triple functional domain protein (PTPRF interacting) " nucleic acid or its complement under low stringency conditions, and/or

(xxxviii) "Vacuolar ATP synthase membrane sector associated protein m8-9 " (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Vacuolar ATP synthase membrane sector associated protein m8-9 ", the variant being encoded by a nucleic acid that

hybridizes to the "Vacuolar ATP synthase membrane sector associated protein m8-9 " nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the gamma-secretase activity and assembly (trafficking) of, or protein composition of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins:

(i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(ii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being

encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,

(v) "Brain-specific GTP-binding protein " (SEQ ID No:187) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Brain-specific GTP-binding protein ", the variant being encoded by a nucleic acid that hybridizes to the "Brain-specific GTP-binding protein " nucleic acid or its complement under low stringency conditions,

(vi) "CGI-13" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "CGI-13", the variant being encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,

(vii) "Cerebral protein-10 " (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Cerebral protein-10 ", the variant being encoded by a nucleic acid that hybridizes to the "Cerebral protein-10 " nucleic acid or its complement under low stringency conditions,

(viii) "Dihydrofolate reductase " (SEQ ID No:188) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dihydrofolate reductase ", the variant being encoded by a nucleic acid that hybridizes to the "Dihydrofolate reductase " nucleic acid or its complement under low stringency conditions,

(ix) "Endocytic receptor Endo180" (SEQ ID No:189) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Endocytic receptor Endo180", the variant being encoded by a nucleic acid that hybridizes to the "Endocytic receptor Endo180" nucleic acid or its complement under low stringency conditions,

(x) "FLJ13660" (SEQ ID No:190) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ13660", the variant being encoded by a nucleic acid that hybridizes to the "FLJ13660" nucleic acid or its complement under low stringency conditions,

- (xi) "HU-K4" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4" nucleic acid or its complement under low stringency conditions,
- (xii) "Integral membrane protein 2B (ITM2B) " (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B) ", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B) " nucleic acid or its complement under low stringency conditions,
- (xiii) "KIAA0062" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0062", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0062" nucleic acid or its complement under low stringency conditions,
- (xiv) "KIAA0251" (SEQ ID No:191) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0251", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0251" nucleic acid or its complement under low stringency conditions,
- (xv) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xvi) "KIAA0971" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0971", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0971" nucleic acid or its complement under low stringency conditions,
- (xvii) "KIAA1250" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1250", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions,
- (xviii) "Mesenchymal stem cell protein DSCD75" (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Mesenchymal stem cell protein DSCD75", the variant being encoded by a nucleic acid that hybridizes to the "Mesenchymal stem cell protein DSCD75" nucleic acid or its complement under low stringency conditions,

(xix) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xx) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a

functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(xxi) "PP2C gamma" (SEQ ID No:195) or a functionally active derivative thereof, or a

functionally active fragment thereof, or a homologue thereof, or a variant of "PP2C

gamma", the variant being encoded by a nucleic acid that hybridizes to the "PP2C gamma" nucleic acid or its complement under low stringency conditions,

(xxii) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,

(xxiii) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,

(xxiv) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions,

(xxv) "Protocadherin 7 " (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Protocadherin 7 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin 7 " nucleic acid or its complement under low stringency conditions,

(xxvi) "Protocadherin beta 16 " (SEQ ID No:197) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 16 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 16 " nucleic acid or its complement under low stringency conditions,

(xxvii) "Protocadherin beta 8 " (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8 " nucleic acid or its complement under low stringency conditions,

(xxviii) "RAB-18" (SEQ ID No:198) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "RAB-18", the variant being encoded by a nucleic acid that hybridizes to the "RAB-18" nucleic acid or its complement under low stringency conditions,

(xxix) "Rab3 GTPase-activating protein, non-catalytic subunit " (SEQ ID No:199) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Rab3 GTPase-activating protein, non-catalytic subunit ", the variant being encoded by a nucleic acid that hybridizes to the "Rab3 GTPase-activating protein, non-catalytic subunit " nucleic acid or its complement under low stringency conditions,

(xxx) "Retinal short-chain dehydrogenase/reductase retSDR2" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Retinal short-chain dehydrogenase/reductase retSDR2", the variant being encoded by a nucleic acid that hybridizes to the "Retinal short-chain dehydrogenase/reductase retSDR2" nucleic acid or its complement under low stringency conditions,

(xxxi) "SMAP-1B" (SEQ ID No:200) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SMAP-1B", the variant being encoded by a nucleic acid that hybridizes to the "SMAP-1B" nucleic acid or its complement under low stringency conditions,

(xxxii) "Sideroflexin 1" (SEQ ID No:201) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sideroflexin 1", the variant being encoded by a nucleic acid that hybridizes to the "Sideroflexin 1" nucleic acid or its complement under low stringency conditions,

(xxxiii) "Signal transducer and activator of transcription-1 " (SEQ ID No:202) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Signal transducer and activator of transcription-1 ", the variant being encoded by a nucleic acid that hybridizes to the "Signal transducer and

activator of transcription-1 " nucleic acid or its complement under low stringency conditions,

(xxxiv) "Sterile alpha and HEAT/Armadillo motif protein" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterile alpha and HEAT/Armadillo motif protein", the variant being encoded by a nucleic acid that hybridizes to the "Sterile alpha and HEAT/Armadillo motif protein" nucleic acid or its complement under low stringency conditions,

(xxxv) "Sterol O-acyltransferase 1 " (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Sterol O-acyltransferase 1 ", the variant being encoded by a nucleic acid that hybridizes to the "Sterol O-acyltransferase 1 " nucleic acid or its complement under low stringency conditions,

(xxxvi) "Thioredoxin domain-containing protein " (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Thioredoxin domain-containing protein ", the variant being encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein " nucleic acid or its complement under low stringency conditions,

(xxxvii) "Triple functional domain protein (PTPRF interacting) " (SEQ ID No:204) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Triple functional domain protein (PTPRF interacting) ", the variant being encoded by a nucleic acid that hybridizes to the "Triple functional domain protein (PTPRF interacting) " nucleic acid or its complement under low stringency conditions, and/or (xxxviii) "Vacuolar ATP synthase membrane sector associated protein m8-9 " (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Vacuolar ATP synthase membrane sector associated protein m8-9 ", the variant being encoded by a nucleic acid that hybridizes to the "Vacuolar ATP synthase membrane sector associated protein m8-9 " nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

The invention further relates to the Aph-1b complex:

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "Aph-1b" (SEQ ID No:208) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1b", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1b" nucleic acid or its complement under low stringency conditions,
    - (ii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
    - (iii) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,
    - (iv) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and
    - (v) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one second protein, which second protein is selected from the group consisting of:
    - (i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,
    - (ii) "23 kDa microsomal signal peptidase subunit" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "23 kDa microsomal signal peptidase subunit", the variant being

encoded by a nucleic acid that hybridizes to the "23 kDa microsomal signal peptidase subunit" nucleic acid or its complement under low stringency conditions,

(iii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(iv) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(v) "Activating transcription factor 6" (SEQ ID No:207) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Activating transcription factor 6", the variant being encoded by a nucleic acid that hybridizes to the "Activating transcription factor 6" nucleic acid or its complement under low stringency conditions,

(vi) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,

(vii) "Autocrine motility factor receptor" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Autocrine motility factor receptor", the variant being encoded by a nucleic acid that hybridizes to the "Autocrine motility factor receptor" nucleic acid or its complement under low stringency conditions,

(viii) "Calsyntenin 1" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin 1", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions,

(ix) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions,

- (x) "FLJ10737" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10737", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10737" nucleic acid or its complement under low stringency conditions,
- (xi) "FLJ14560" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ14560", the variant being encoded by a nucleic acid that hybridizes to the "FLJ14560" nucleic acid or its complement under low stringency conditions,
- (xii) "HU-K4" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4" nucleic acid or its complement under low stringency conditions,
- (xiii) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xiv) "PAS domain containing serine/threonine kinase" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PAS domain containing serine/threonine kinase", the variant being encoded by a nucleic acid that hybridizes to the "PAS domain containing serine/threonine kinase" nucleic acid or its complement under low stringency conditions,
- (xv) "PP2C gamma" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP2C gamma", the variant being encoded by a nucleic acid that hybridizes to the "PP2C gamma" nucleic acid or its complement under low stringency conditions,
- (xvi) "Polycystin 2" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Polycystin 2", the variant being encoded by a nucleic acid that hybridizes to the "Polycystin 2" nucleic acid or its complement under low stringency conditions,
- (xvii) "Protocadherin beta 8a" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8a", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8a" nucleic acid or its complement under low stringency conditions,

(xviii) "Protocadherin gamma C3 " (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin gamma C3 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3 " nucleic acid or its complement under low stringency conditions,

(xix) "Voltage-dependent anion channel 3" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 3", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 3" nucleic acid or its complement under low stringency conditions, and

(xx) "cAMP responsive element binding protein-like 1" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "cAMP responsive element binding protein-like 1", the variant being encoded by a nucleic acid that hybridizes to the "cAMP responsive element binding protein-like 1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. The protein complex according to No. 1 wherein the first protein is the protein "Aph-1b" (SEQ ID No:208), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1b", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1b" nucleic acid under low stringency conditions.

3. The protein complex according to No. 1 comprising the following proteins:

(i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a

nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(ii) "23 kDa microsomal signal peptidase subunit" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "23 kDa microsomal signal peptidase subunit", the variant being encoded by a nucleic acid that hybridizes to the "23 kDa microsomal signal peptidase subunit" nucleic acid or its complement under low stringency conditions,

(iii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(iv) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(v) "Activating transcription factor 6" (SEQ ID No:207) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Activating transcription factor 6", the variant being encoded by a nucleic acid that hybridizes to the "Activating transcription factor 6" nucleic acid or its complement under low stringency conditions,

(vi) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,

(vii) "Aph-1b" (SEQ ID No:208) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1b", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1b" nucleic acid or its complement under low stringency conditions,

(viii) "Autocrine motility factor receptor" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Autocrine motility factor receptor", the variant being encoded by a nucleic acid that hybridizes to the "Autocrine motility factor receptor" nucleic acid or its complement under low stringency conditions,

- (ix) "Calsyntenin 1" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin 1", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions,
- (x) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions,
- (xi) "FLJ10737" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10737", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10737" nucleic acid or its complement under low stringency conditions,
- (xii) "FLJ14560" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ14560", the variant being encoded by a nucleic acid that hybridizes to the "FLJ14560" nucleic acid or its complement under low stringency conditions,
- (xiii) "HU-K4" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4" nucleic acid or its complement under low stringency conditions,
- (xiv) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xv) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (xvi) "PAS domain containing serine/threonine kinase" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PAS domain containing serine/threonine kinase", the variant being encoded by a nucleic acid that hybridizes to the "PAS domain containing serine/threonine kinase" nucleic acid or its complement under low stringency conditions,

(xvii) "PP2C gamma" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP2C gamma", the variant being encoded by a nucleic acid that hybridizes to the "PP2C gamma" nucleic acid or its complement under low stringency conditions,

(xviii) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,

(xix) "Polycystin 2" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Polycystin 2", the variant being encoded by a nucleic acid that hybridizes to the "Polycystin 2" nucleic acid or its complement under low stringency conditions,

(xx) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,

(xxi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions,

(xxii) "Protocadherin beta 8a" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8a", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8a" nucleic acid or its complement under low stringency conditions,

(xxiii) "Protocadherin gamma C3 " (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin gamma C3 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3 " nucleic acid or its complement under low stringency conditions,

(xxiv) "Voltage-dependent anion channel 3" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 3", the variant being encoded by a nucleic

acid that hybridizes to the "Voltage-dependent anion channel 3" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "cAMP responsive element binding protein-like 1" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "cAMP responsive element binding protein-like 1", the variant being encoded by a nucleic acid that hybridizes to the "cAMP responsive element binding protein-like 1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising at least 6 but no more than 24 of the following proteins:

(i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(ii) "23 kDa microsomal signal peptidase subunit" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "23 kDa microsomal signal peptidase subunit", the variant being encoded by a nucleic acid that hybridizes to the "23 kDa microsomal signal peptidase subunit" nucleic acid or its complement under low stringency conditions,

(iii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(iv) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(v) "Activating transcription factor 6" (SEQ ID No:207) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Activating transcription factor 6", the variant being encoded by a nucleic acid that hybridizes to the "Activating transcription factor 6" nucleic acid or its complement under low stringency conditions,

- (vi) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,
- (vii) "Aph-1b" (SEQ ID No:208) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1b", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1b" nucleic acid or its complement under low stringency conditions,
- (viii) "Autocrine motility factor receptor" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Autocrine motility factor receptor", the variant being encoded by a nucleic acid that hybridizes to the "Autocrine motility factor receptor" nucleic acid or its complement under low stringency conditions,
- (ix) "Calsyntenin 1" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin 1", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions,
- (x) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions,
- (xi) "FLJ10737" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10737", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10737" nucleic acid or its complement under low stringency conditions,
- (xii) "FLJ14560" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ14560", the variant being encoded by a nucleic acid that hybridizes to the "FLJ14560" nucleic acid or its complement under low stringency conditions,
- (xiii) "HU-K4" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4" nucleic acid or its complement under low stringency conditions,

- (xiv) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xv) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (xvi) "PAS domain containing serine/threonine kinase" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PAS domain containing serine/threonine kinase", the variant being encoded by a nucleic acid that hybridizes to the "PAS domain containing serine/threonine kinase" nucleic acid or its complement under low stringency conditions,
- (xvii) "PP2C gamma" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP2C gamma", the variant being encoded by a nucleic acid that hybridizes to the "PP2C gamma" nucleic acid or its complement under low stringency conditions,
- (xviii) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,
- (xix) "Polycystin 2" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Polycystin 2", the variant being encoded by a nucleic acid that hybridizes to the "Polycystin 2" nucleic acid or its complement under low stringency conditions,
- (xx) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,
- (xxi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions,

(xxii) "Protocadherin beta 8a" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8a", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8a" nucleic acid or its complement under low stringency conditions,

(xxiii) "Protocadherin gamma C3 " (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin gamma C3 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3 " nucleic acid or its complement under low stringency conditions,

(xxiv) "Voltage-dependent anion channel 3" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 3", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 3" nucleic acid or its complement under low stringency conditions,

(xxv) "cAMP responsive element binding protein-like 1" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "cAMP responsive element binding protein-like 1", the variant being encoded by a nucleic acid that hybridizes to the "cAMP responsive element binding protein-like 1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the gamma-secretase activity and assembly (trafficking).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:  
expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Aph-1b complex obtainable by a process according to any of No. 9 - 11.
13. Protein of the Aph-1b complex selected from  
(i) "Autocrine motility factor receptor" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Autocrine motility factor receptor", the variant being encoded by a nucleic acid that hybridizes to the "Autocrine motility factor receptor" nucleic acid or its complement under low stringency conditions,  
(ii) "FLJ10737" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10737", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10737" nucleic acid or its complement under low stringency conditions,  
(iii) "FLJ14560" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ14560", the variant being encoded by a nucleic acid that hybridizes to the "FLJ14560" nucleic acid or its complement under low stringency conditions,

- (iv) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (v) "Protocadherin beta 8a" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8a", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8a" nucleic acid or its complement under low stringency conditions, and
- (vi) "Protocadherin gamma C3 " (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin gamma C3 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3 " nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising:

- (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
- (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b) or
- (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or

a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container:

(a) the complex of any of No. 1 - 8 and/or the proteins of No. 13 and/or

(b) an antibody according to No. 17 and/or

(c) a nucleic acid encoding a protein of the complex of any of No. 1 - 8 and/or a protein of No. 13 and/or

(d) cells expressing the complex of any of No. 1 - 8 and/or a protein of No. 13 and, optionally,

(e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for modifying a physiological substrate of the complex comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "Autocrine motility factor receptor" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Autocrine motility factor receptor", the variant being encoded by a nucleic acid that hybridizes to the "Autocrine motility factor receptor" nucleic acid or its complement under low stringency conditions,
- (ii) "FLJ10737" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10737", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10737" nucleic acid or its complement under low stringency conditions,
- (iii) "FLJ14560" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ14560", the variant being encoded by a nucleic acid that hybridizes to the "FLJ14560" nucleic acid or its complement under low stringency conditions,
- (iv) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (v) "Protocadherin beta 8a" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8a", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8a" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "Protocadherin gamma C3 " (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin gamma C3 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3 " nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to a complex of anyone of No. 1 - 8 and/or any of the following the proteins:

- (i) "Autocrine motility factor receptor" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Autocrine motility factor receptor", the variant being encoded by a nucleic acid that hybridizes to the "Autocrine motility factor receptor" nucleic acid or its complement under low stringency conditions,
- (ii) "FLJ10737" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10737", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10737" nucleic acid or its complement under low stringency conditions,
- (iii) "FLJ14560" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ14560", the variant being encoded by a nucleic acid that hybridizes to the "FLJ14560" nucleic acid or its complement under low stringency conditions,
- (iv) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (v) "Protocadherin beta 8a" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8a", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8a" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "Protocadherin gamma C3 " (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin gamma C3 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3 " nucleic acid or its complement under low stringency conditions, comprising the steps of:

- (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and
- (b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:

- (a) exposing said complex, or a cell or organism containing Aph-1b complex to one or more candidate molecules; and
- (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex regulated by the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether
- (i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "23 kDa microsomal signal peptidase subunit" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "23 kDa microsomal signal peptidase subunit", the variant being encoded by a nucleic acid that hybridizes to the "23 kDa microsomal signal peptidase subunit" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
  - (v) "Activating transcription factor 6" (SEQ ID No:207) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Activating transcription factor 6", the variant being encoded by a nucleic acid that hybridizes to the "Activating transcription factor 6" nucleic acid or its complement under low stringency conditions, and/or
  - (vi) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions, and/or
  - (vii) "Aph-1b" (SEQ ID No:208) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1b", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1b" nucleic acid or its complement under low stringency conditions, and/or

- (viii) "Autocrine motility factor receptor" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Autocrine motility factor receptor", the variant being encoded by a nucleic acid that hybridizes to the "Autocrine motility factor receptor" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Calsyntenin 1" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin 1", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions, and/or
- (x) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "FLJ10737" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10737", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10737" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "FLJ14560" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ14560", the variant being encoded by a nucleic acid that hybridizes to the "FLJ14560" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "HU-K4" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

- (xvi) "PAS domain containing serine/threonine kinase" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PAS domain containing serine/threonine kinase", the variant being encoded by a nucleic acid that hybridizes to the "PAS domain containing serine/threonine kinase" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "PP2C gamma" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP2C gamma", the variant being encoded by a nucleic acid that hybridizes to the "PP2C gamma" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "Polycystin 2" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Polycystin 2", the variant being encoded by a nucleic acid that hybridizes to the "Polycystin 2" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "Protocadherin beta 8a" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8a", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8a" nucleic acid or its complement under low stringency conditions, and/or
- (xxiii) "Protocadherin gamma C3 " (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin gamma C3 ", the variant being encoded by a nucleic acid that hybridizes

to the "Protocadherin gamma C3 " nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "Voltage-dependent anion channel 3" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 3", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 3" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "cAMP responsive element binding protein-like 1" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "cAMP responsive element binding protein-like 1", the variant being encoded by a nucleic acid that hybridizes to the "cAMP responsive element binding protein-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the

complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether:

- (i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions, and/or
- (ii) "23 kDa microsomal signal peptidase subunit" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "23 kDa microsomal signal peptidase subunit", the variant being encoded by a nucleic acid that hybridizes to the "23 kDa microsomal signal peptidase subunit" nucleic acid or its complement under low stringency conditions, and/or

- (iii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions, and/or
- (iv) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (v) "Activating transcription factor 6" (SEQ ID No:207) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Activating transcription factor 6", the variant being encoded by a nucleic acid that hybridizes to the "Activating transcription factor 6" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "Aph-1b" (SEQ ID No:208) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1b", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1b" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "Autocrine motility factor receptor" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Autocrine motility factor receptor", the variant being encoded by a nucleic acid that hybridizes to the "Autocrine motility factor receptor" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Calsyntenin 1" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin 1", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions, and/or
- (x) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1

catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions, and/or

(xi) "FLJ10737" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10737", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10737" nucleic acid or its complement under low stringency conditions, and/or

(xii) "FLJ14560" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ14560", the variant being encoded by a nucleic acid that hybridizes to the "FLJ14560" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "HU-K4" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions, and/or

(xv) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "PAS domain containing serine/threonine kinase" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PAS domain containing serine/threonine kinase", the variant being encoded by a nucleic acid that hybridizes to the "PAS domain containing serine/threonine kinase" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "PP2C gamma" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP2C gamma", the variant being encoded by a nucleic acid that hybridizes to the "PP2C gamma" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being

encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions, and/or

(xix) "Polycystin 2" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Polycystin 2", the variant being encoded by a nucleic acid that hybridizes to the "Polycystin 2" nucleic acid or its complement under low stringency conditions, and/or

(xx) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "Protocadherin beta 8a" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8a", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8a" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "Protocadherin gamma C3 " (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin gamma C3 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3 " nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "Voltage-dependent anion channel 3" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 3", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 3" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "cAMP responsive element binding protein-like 1" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "cAMP responsive element binding protein-like 1", the variant being encoded by a nucleic acid that hybridizes to the "cAMP responsive element

binding protein-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the gamma-secretase activity and assembly (trafficking) of, or protein composition of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins  
(i) "18 kDa microsomal signal peptidase subunit " (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "18 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "18 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(ii) "23 kDa microsomal signal peptidase subunit" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "23 kDa microsomal signal peptidase subunit", the variant being encoded by a nucleic acid that hybridizes to the "23 kDa microsomal signal peptidase subunit" nucleic acid or its complement under low stringency conditions,

(iii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue

thereof, or a variant of "25 kDa microsomal signal peptidase subunit ", the variant being encoded by a nucleic acid that hybridizes to the "25 kDa microsomal signal peptidase subunit " nucleic acid or its complement under low stringency conditions,

(iv) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(v) "Activating transcription factor 6" (SEQ ID No:207) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Activating transcription factor 6", the variant being encoded by a nucleic acid that hybridizes to the "Activating transcription factor 6" nucleic acid or its complement under low stringency conditions,

(vi) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,

(vii) "Aph-1b" (SEQ ID No:208) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1b", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1b" nucleic acid or its complement under low stringency conditions,

(viii) "Autocrine motility factor receptor" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Autocrine motility factor receptor", the variant being encoded by a nucleic acid that hybridizes to the "Autocrine motility factor receptor" nucleic acid or its complement under low stringency conditions,

(ix) "Calsyntenin 1" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsyntenin 1", the variant being encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions,

(x) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions,

- (xi) "FLJ10737" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10737", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10737" nucleic acid or its complement under low stringency conditions,
- (xii) "FLJ14560" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ14560", the variant being encoded by a nucleic acid that hybridizes to the "FLJ14560" nucleic acid or its complement under low stringency conditions,
- (xiii) "HU-K4" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "HU-K4", the variant being encoded by a nucleic acid that hybridizes to the "HU-K4" nucleic acid or its complement under low stringency conditions,
- (xiv) "KIAA0363" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0363", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xv) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (xvi) "PAS domain containing serine/threonine kinase" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PAS domain containing serine/threonine kinase", the variant being encoded by a nucleic acid that hybridizes to the "PAS domain containing serine/threonine kinase" nucleic acid or its complement under low stringency conditions,
- (xvii) "PP2C gamma" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PP2C gamma", the variant being encoded by a nucleic acid that hybridizes to the "PP2C gamma" nucleic acid or its complement under low stringency conditions,
- (xviii) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,

- (xix) "Polycystin 2" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Polycystin 2", the variant being encoded by a nucleic acid that hybridizes to the "Polycystin 2" nucleic acid or its complement under low stringency conditions,
- (xx) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,
- (xxi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions,
- (xxii) "Protocadherin beta 8a" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 8a", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 8a" nucleic acid or its complement under low stringency conditions,
- (xxiii) "Protocadherin gamma C3 " (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin gamma C3 ", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3 " nucleic acid or its complement under low stringency conditions,
- (xxiv) "Voltage-dependent anion channel 3" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Voltage-dependent anion channel 3", the variant being encoded by a nucleic acid that hybridizes to the "Voltage-dependent anion channel 3" nucleic acid or its complement under low stringency conditions, and/or
- (xxv) "cAMP responsive element binding protein-like 1" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "cAMP responsive element binding protein-like 1", the variant being encoded by a nucleic acid that hybridizes to the "cAMP responsive element binding protein-like 1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or

disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

The invention further relates to the Pen-2 complex:

1. A protein complex selected from complex (I) and comprising:
  - (a) at least one first protein selected from the group consisting of:
    - (i) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,
    - (ii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
    - (iii) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions, and
    - (iv) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one second protein, which second protein is selected from the group consisting of:
    - (i) "Alpha-2 catenin" (SEQ ID No:218) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha-2 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha-2 catenin" nucleic acid or its complement under low stringency conditions,
    - (ii) "Copine III" (SEQ ID No:219) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Copine III", the variant being encoded by a nucleic acid that hybridizes to the "Copine III" nucleic acid or its complement under low stringency conditions,

- (iii) "Dachshund 2" (SEQ ID No:220) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dachshund 2", the variant being encoded by a nucleic acid that hybridizes to the "Dachshund 2" nucleic acid or its complement under low stringency conditions,
- (iv) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions,
- (v) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,
- (vi) "MGC2803" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC2803", the variant being encoded by a nucleic acid that hybridizes to the "MGC2803" nucleic acid or its complement under low stringency conditions,
- (vii) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions,
- (viii) "TNRC15" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "TNRC15", the variant being encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions,
- (ix) "TPST1" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "TPST1", the variant being encoded by a nucleic acid that hybridizes to the "TPST1" nucleic acid or its complement under low stringency conditions, and
- (x) "ZIP kinase" (SEQ ID No:225) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ZIP kinase", the variant being encoded by a nucleic acid that hybridizes to the "ZIP kinase" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5),

5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. The protein complex according to No. 1 wherein the first protein is the protein "Pen-2" (SEQ ID No:15), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid under low stringency conditions.

3. The protein complex according to No. 1 comprising the following proteins:

- (i) "Alpha-2 catenin" (SEQ ID No:218) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha-2 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha-2 catenin" nucleic acid or its complement under low stringency conditions,
- (ii) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,
- (iii) "Copine III" (SEQ ID No:219) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Copine III", the variant being encoded by a nucleic acid that hybridizes to the "Copine III" nucleic acid or its complement under low stringency conditions,
- (iv) "Dachshund 2" (SEQ ID No:220) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dachshund 2", the variant being encoded by a nucleic acid that hybridizes to the "Dachshund 2" nucleic acid or its complement under low stringency conditions,
- (v) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions,

- (vi) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,
- (vii) "MGC2803" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC2803", the variant being encoded by a nucleic acid that hybridizes to the "MGC2803" nucleic acid or its complement under low stringency conditions,
- (viii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (ix) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,
- (x) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,
- (xi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions,
- (xii) "TNRC15" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "TNRC15", the variant being encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions,
- (xiii) "TPST1" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "TPST1", the variant being encoded by a nucleic acid that hybridizes to the "TPST1" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "ZIP kinase" (SEQ ID No:225) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ZIP kinase",

the variant being encoded by a nucleic acid that hybridizes to the "ZIP kinase" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising at least 5 but no more than 13 of the following proteins:

- (i) "Alpha-2 catenin" (SEQ ID No:218) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha-2 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha-2 catenin" nucleic acid or its complement under low stringency conditions,
- (ii) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,
- (iii) "Copine III" (SEQ ID No:219) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Copine III", the variant being encoded by a nucleic acid that hybridizes to the "Copine III" nucleic acid or its complement under low stringency conditions,
- (iv) "Dachshund 2" (SEQ ID No:220) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dachshund 2", the variant being encoded by a nucleic acid that hybridizes to the "Dachshund 2" nucleic acid or its complement under low stringency conditions,
- (v) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions,
- (vi) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,
- (vii) "MGC2803" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC2803", the variant being encoded by a nucleic acid that hybridizes to the "MGC2803" nucleic acid or its complement under low stringency conditions,

- (viii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (ix) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,
- (x) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,
- (xi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions,
- (xii) "TNRC15" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "TNRC15", the variant being encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions,
- (xiii) "TPST1" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "TPST1", the variant being encoded by a nucleic acid that hybridizes to the "TPST1" nucleic acid or its complement under low stringency conditions,
- (xiv) "ZIP kinase" (SEQ ID No:225) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ZIP kinase", the variant being encoded by a nucleic acid that hybridizes to the "ZIP kinase" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the gamma-secretase activity and assembly (trafficking).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:

expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Pen-2 complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the Pen-2 complex selected from

- (i) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,
- (ii) "MGC2803" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC2803",

the variant being encoded by a nucleic acid that hybridizes to the "MGC2803" nucleic acid or its complement under low stringency conditions, and

(iii) "TNRC15" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "TNRC15", the variant being encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising:

- (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
- (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b) or
- (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according

to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container:

- (a) the complex of any of No. 1 - 8 and/or the proteins of No. 13 and/or
- (b) an antibody according to No. 17 and/or
- (c) a nucleic acid encoding a protein of the complex of any of No. 1 - 8 and/or a protein of No. 13 and/or
- (d) cells expressing the complex of any of No. 1 - 8 and/or a protein of No. 13 and, optionally,
- (e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for modifying a physiological substrate of the complex comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,
- (ii) "MGC2803" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC2803", the variant being encoded by a nucleic acid that hybridizes to the "MGC2803" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "TNRC15" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "TNRC15", the variant being encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to a complex of anyone of No. 1 - 8 and/or any of the following the proteins:

- (i) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,
- (ii) "MGC2803" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC2803", the variant being encoded by a nucleic acid that hybridizes to the "MGC2803" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "TNRC15" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "TNRC15", the variant being encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions, comprising the steps of:
  - (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:

(a) exposing said complex, or a cell or organism containing Pen-2 complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex regulated by the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether

- (i) "Alpha-2 catenin" (SEQ ID No:218) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha-2 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha-2 catenin" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "Copine III" (SEQ ID No:219) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Copine III", the variant being encoded by a nucleic acid that hybridizes to the "Copine III" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Dachshund 2" (SEQ ID No:220) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dachshund 2", the variant being encoded by a nucleic acid that hybridizes to the "Dachshund 2" nucleic acid or its complement under low stringency conditions, and/or
- (v) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "MGC2803" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC2803", the variant being encoded by a nucleic acid that hybridizes to the "MGC2803" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being

encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions, and/or

(x) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and/or

(xi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions, and/or

(xii) "TNRC15" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "TNRC15", the variant being encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "TPST1" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "TPST1", the variant being encoded by a nucleic acid that hybridizes to the "TPST1" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "ZIP kinase" (SEQ ID No:225) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ZIP kinase", the variant being encoded by a nucleic acid that hybridizes to the "ZIP kinase" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity,

composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether (i) "Alpha-2 catenin" (SEQ ID No:218) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha-2

- catenin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha-2 catenin" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "Copine III" (SEQ ID No:219) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Copine III", the variant being encoded by a nucleic acid that hybridizes to the "Copine III" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Dachshund 2" (SEQ ID No:220) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dachshund 2", the variant being encoded by a nucleic acid that hybridizes to the "Dachshund 2" nucleic acid or its complement under low stringency conditions, and/or
- (v) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "MGC2803" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC2803", the variant being encoded by a nucleic acid that hybridizes to the "MGC2803" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions, and/or

- (x) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "TNRC15" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "TNRC15", the variant being encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "TPST1" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "TPST1", the variant being encoded by a nucleic acid that hybridizes to the "TPST1" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "ZIP kinase" (SEQ ID No:225) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ZIP kinase", the variant being encoded by a nucleic acid that hybridizes to the "ZIP kinase" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the gamma-secretase activity and assembly (trafficking) of, or protein composition of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins:

(i) "Alpha-2 catenin" (SEQ ID No:218) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha-2 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha-2 catenin" nucleic acid or its complement under low stringency conditions,

(ii) "Aph-1a" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Aph-1a", the variant being encoded by a nucleic acid that hybridizes to the "Aph-1a" nucleic acid or its complement under low stringency conditions,

(iii) "Copine III" (SEQ ID No:219) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Copine III", the variant being encoded by a nucleic acid that hybridizes to the "Copine III" nucleic acid or its complement under low stringency conditions,

(iv) "Dachshund 2" (SEQ ID No:220) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dachshund 2", the variant being encoded by a nucleic acid that hybridizes to the "Dachshund 2" nucleic acid or its complement under low stringency conditions,

(v) "Delta-1 catenin" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-1 catenin", the variant being encoded by a nucleic acid that hybridizes to the "Delta-1 catenin" nucleic acid or its complement under low stringency conditions,

(vi) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,

(vii) "MGC2803" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC2803",

the variant being encoded by a nucleic acid that hybridizes to the "MGC2803" nucleic acid or its complement under low stringency conditions,

(viii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(ix) "Pen-2" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Pen-2", the variant being encoded by a nucleic acid that hybridizes to the "Pen-2" nucleic acid or its complement under low stringency conditions,

(x) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,

(xi) "Presenilin 2" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 2", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 2" nucleic acid or its complement under low stringency conditions,

(xii) "TNRC15" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "TNRC15", the variant being encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions,

(xiii) "TPST1" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "TPST1", the variant being encoded by a nucleic acid that hybridizes to the "TPST1" nucleic acid or its complement under low stringency conditions, and/or (xiv) "ZIP kinase" (SEQ ID No:225) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ZIP kinase", the variant being encoded by a nucleic acid that hybridizes to the "ZIP kinase" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

The invention further relates to the APP complex:

1. A protein complex selected from complex (I) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(ii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(iv) "JIP-1" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "JIP-1", the variant being encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions, and

(v) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

(i) "Bcl-XL-binding protein v68 " (SEQ ID No:226) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Bcl-XL-binding protein v68 ", the variant being encoded by a nucleic acid that hybridizes to the "Bcl-XL-binding protein v68 " nucleic acid or its complement under low stringency conditions,

(ii) "FLJ10773" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773",

the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773" nucleic acid or its complement under low stringency conditions,

(iii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(iv) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions, and

(v) "S-100 beta" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. The protein complex according to No. 1 wherein the first protein is the protein "APP" (SEQ ID No:29), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" under low stringency conditions.

3. The protein complex according to No. 1 comprising the following proteins:

(i) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(ii) "Bcl-XL-binding protein v68 " (SEQ ID No:226) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

- "Bcl-XL-binding protein v68 ", the variant being encoded by a nucleic acid that hybridizes to the "Bcl-XL-binding protein v68 " nucleic acid or its complement under low stringency conditions,
- (iii) "FLJ10773" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (v) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (vi) "JIP-1" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "JIP-1", the variant being encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions,
- (vii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (viii) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions,
- (ix) "S-100 beta" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions, and/or
- (x) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant

being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising at least 6 but no more than 9 of the following proteins:

- (i) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (ii) "Bcl-XL-binding protein v68 " (SEQ ID No:226) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Bcl-XL-binding protein v68 ", the variant being encoded by a nucleic acid that hybridizes to the "Bcl-XL-binding protein v68 " nucleic acid or its complement under low stringency conditions,
- (iii) "FLJ10773" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (v) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (vi) "JIP-1" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "JIP-1", the variant being encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions,
- (vii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

- (viii) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions,
- (ix) "S-100 beta" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions,
- (x) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the signalling activity (regulation of transcription).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:  
expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the bait protein,

and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the APP complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the APP complex selected from

(i) "FLJ10773" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising:

(a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or

(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said

proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b) or  
 (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 – 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container:

- (a) the complex of any of No. 1 – 8 and/or the proteins of No. 13 and/or
- (b) an antibody according to No. 17 and/or
- (c) a nucleic acid encoding a protein of the complex of any of No. 1 – 8 and/or a protein of No. 13 and/or
- (d) cells expressing the complex of any of No. 1 – 8 and/or a protein of No. 13 and, optionally,
- (e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for modifying a physiological substrate of the complex comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "FLJ10773" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to a complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "FLJ10773" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773" nucleic acid or its complement under low stringency conditions, comprising the steps of:

(a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:

(a) exposing said complex, or a cell or organism containing APP complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex regulated by the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether  
 (i) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or  
 (ii) "Bcl-XL-binding protein v68 " (SEQ ID No:226) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Bcl-XL-binding protein v68 ", the variant being encoded by a nucleic acid that hybridizes to the "Bcl-XL-binding protein v68 " nucleic acid or its complement under low stringency conditions, and/or

(iii) "FLJ10773" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

(v) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or

(vi) "JIP-1" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "JIP-1", the variant being encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions, and/or

(vii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(viii) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions, and/or

(ix) "S-100 beta" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions, and/or

(x) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant

being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether (i) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Bcl-XL-binding protein v68 " (SEQ ID No:226) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Bcl-XL-binding protein v68 ", the variant being encoded by a nucleic acid that hybridizes to the "Bcl-XL-binding protein v68 " nucleic acid or its complement under low stringency conditions, and/or

(iii) "FLJ10773" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

(v) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or

(vi) "JIP-1" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "JIP-1", the variant being

encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions, and/or

(vii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(viii) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions, and/or

(ix) "S-100 beta" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions, and/or

(x) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the signalling activity (regulation of transcription) of, or protein composition of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins:

- (i) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (ii) "Bcl-XL-binding protein v68 " (SEQ ID No:226) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Bcl-XL-binding protein v68 ", the variant being encoded by a nucleic acid that hybridizes to the "Bcl-XL-binding protein v68 " nucleic acid or its complement under low stringency conditions,
- (iii) "FLJ10773" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (v) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (vi) "JIP-1" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "JIP-1", the variant being encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions,
- (vii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(viii) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions,

(ix) "S-100 beta" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions, and/or(x) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

The invention further relates to the APP695SW complex:

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "APP695SW" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP695SW", the variant being encoded by a nucleic acid that hybridizes to the "APP695SW" nucleic acid or its complement under low stringency conditions,
    - (ii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
    - (iii) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(iv) "JIP-1" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "JIP-1", the variant being encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions, and

(v) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

(i) "FLJ10773 " (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773 ", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773 " nucleic acid or its complement under low stringency conditions,

(ii) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B)", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B)" nucleic acid or its complement under low stringency conditions, and

(iii) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. The protein complex according to No. 1 wherein the first protein is the protein "APP695SW" (SEQ ID No:232), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"APP695SW", the variant being encoded by a nucleic acid that hybridizes to the "APP695SW" nucleic acid under low stringency conditions.

3. The protein complex according to No. 1 comprising the following proteins:

- (i) "APP695SW" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP695SW", the variant being encoded by a nucleic acid that hybridizes to the "APP695SW" nucleic acid or its complement under low stringency conditions,
- (ii) "FLJ10773 " (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773 ", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773 " nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (v) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B)", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B)" nucleic acid or its complement under low stringency conditions,
- (vi) "JIP-1" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "JIP-1", the variant being encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions,
- (vii) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions, and/or

(viii) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions,

and a protein complex selected from complex (II) and comprising the following proteins:

(i) "APP695SW" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP695SW", the variant being encoded by a nucleic acid that hybridizes to the "APP695SW" nucleic acid or its complement under low stringency conditions,

(ii) "FLJ10773" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B)", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B)" nucleic acid or its complement under low stringency conditions,

(vi) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions, and/or

(vii) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions,

and a protein complex selected from complex (III) and comprising the following proteins:

- (i) "APP695SW" (SEQ ID No:232) or a functionally active derivative thereof,
- (ii) "FLJ10773 " (SEQ ID No:227) or a functionally active derivative thereof,
- (iii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof,
- (iv) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof,
- (v) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:35) or a functionally active derivative thereof,
- (vi) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, and
- (vii) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof,

4. The protein complex according to No. 1 comprising at least 6 but no more than 7 of the following proteins:

- (i) "APP695SW" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP695SW", the variant being encoded by a nucleic acid that hybridizes to the "APP695SW" nucleic acid or its complement under low stringency conditions,
- (ii) "FLJ10773 " (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773 ", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773 " nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (v) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B)", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B)" nucleic acid or its complement under low stringency conditions,

(vi) "JIP-1" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "JIP-1", the variant being encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions,

(vii) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions,

(viii) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the signalling activity (regulation of transcription).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:

expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the bait protein,

and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the APP695SW complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the APP695SW complex selected from

(i) "FLJ10773 " (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773 ", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773 " nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising:

- (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
- (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said

proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b) or (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container:

- (a) the complex of any of No. 1 – 8 and/or the proteins of No. 13 and/or
- (b) an antibody according to No. 17 and/or
- (c) a nucleic acid encoding a protein of the complex of any of No. 1 – 8 and/or a protein of No. 13 and/or
- (d) cells expressing the complex of any of No. 1 – 8 and/or a protein of No. 13 and, optionally,
- (e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for modifying a physiological substrate of the complex comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "FLJ10773 " (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773 ", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773 " nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to a complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "FLJ10773 " (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773 ", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773 " nucleic acid or its complement under low stringency conditions, comprising the steps of:

(a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determininig whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:

- (a) exposing said complex, or a cell or organism containing APP695SW complex to one or more candidate molecules; and
- (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex regulated by the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether

- (i) "APP695SW" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP695SW", the variant being encoded by a nucleic acid that hybridizes to the "APP695SW" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "FLJ10773 " (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773 ",

the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773 " nucleic acid or its complement under low stringency conditions, and/or

(iii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or

(v) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B)", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B)" nucleic acid or its complement under low stringency conditions, and/or

(vi) "JIP-1" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "JIP-1", the variant being encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions, and/or

(vii) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions, and/or

(viii) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament

for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether

- (i) "APP695SW" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP695SW", the variant being encoded by a nucleic acid that hybridizes to the "APP695SW" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "FLJ10773 " (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773 ", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773 " nucleic acid or its complement under low stringency conditions, and/or
- (iii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B)", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B)" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "JIP-1" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "JIP-1", the variant being encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta",

the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the signalling activity (regulation of transcription) of, or protein composition of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins:

- (i) "APP695SW" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP695SW", the variant being encoded by a nucleic acid that hybridizes to the "APP695SW" nucleic acid or its complement under low stringency conditions,
- (ii) "FLJ10773 " (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "FLJ10773 ", the variant being encoded by a nucleic acid that hybridizes to the "FLJ10773 " nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

- (iv) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (v) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane protein 2B (ITM2B)", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B)" nucleic acid or its complement under low stringency conditions,
- (vi) "JIP-1" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "JIP-1", the variant being encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions,
- (vii) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions, and/or(viii) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

The invention further relates to the APP-C99 complex:

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "APP-C99" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP-C99", the variant being encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(ii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and

(iv) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

(i) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(ii) "Delta-like homologue" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-like homologue", the variant being encoded by a nucleic acid that hybridizes to the "Delta-like homologue" nucleic acid or its complement under low stringency conditions,

(iii) "Integral membrane transporter protein" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane transporter protein", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane transporter protein" nucleic acid or its complement under low stringency conditions,

(iv) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,

(v) "KIAA1949" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1949",

the variant being encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,

(vi) "MGC4022" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4022", the variant being encoded by a nucleic acid that hybridizes to the "MGC4022" nucleic acid or its complement under low stringency conditions,

(vii) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,

(viii) "NAP-1 related protein" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NAP-1 related protein", the variant being encoded by a nucleic acid that hybridizes to the "NAP-1 related protein" nucleic acid or its complement under low stringency conditions,

(ix) "Neurocalcin delta" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurocalcin delta", the variant being encoded by a nucleic acid that hybridizes to the "Neurocalcin delta" nucleic acid or its complement under low stringency conditions,

(x) "REST corepressor" (SEQ ID No:239) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "REST corepressor", the variant being encoded by a nucleic acid that hybridizes to the "REST corepressor" nucleic acid or its complement under low stringency conditions,

(xi) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions, and

(xii) "S-100 beta" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer

consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. The protein complex according to No. 1 wherein the first protein is the protein "APP-C99" (SEQ ID No:30), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP-C99", the variant being encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid under low stringency conditions.

3. The protein complex according to No. 1 comprising the following proteins:

- (i) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (ii) "APP-C99" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP-C99", the variant being encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iii) "Delta-like homologue" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-like homologue", the variant being encoded by a nucleic acid that hybridizes to the "Delta-like homologue" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (v) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (vi) "Integral membrane transporter protein" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane transporter protein", the variant being encoded by a

nucleic acid that hybridizes to the "Integral membrane transporter protein" nucleic acid or its complement under low stringency conditions,

(vii) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,

(viii) "KIAA1949" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1949", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,

(ix) "MGC4022" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4022", the variant being encoded by a nucleic acid that hybridizes to the "MGC4022" nucleic acid or its complement under low stringency conditions,

(x) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,

(xi) "NAP-1 related protein" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NAP-1 related protein", the variant being encoded by a nucleic acid that hybridizes to the "NAP-1 related protein" nucleic acid or its complement under low stringency conditions,

(xii) "Neurocalcin delta" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurocalcin delta", the variant being encoded by a nucleic acid that hybridizes to the "Neurocalcin delta" nucleic acid or its complement under low stringency conditions,

(xiii) "REST corepressor" (SEQ ID No:239) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "REST corepressor", the variant being encoded by a nucleic acid that hybridizes to the "REST corepressor" nucleic acid or its complement under low stringency conditions,

(xiv) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions,

(xv) "S-100 beta" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising at least 4 but no more than 15 of the following proteins:

(i) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(ii) "APP-C99" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP-C99", the variant being encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iii) "Delta-like homologue" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-like homologue", the variant being encoded by a nucleic acid that hybridizes to the "Delta-like homologue" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(v) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(vi) "Integral membrane transporter protein" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane transporter protein", the variant being encoded by a

nucleic acid that hybridizes to the "Integral membrane transporter protein" nucleic acid or its complement under low stringency conditions,

(vii) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,

(viii) "KIAA1949" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1949", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,

(ix) "MGC4022" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4022", the variant being encoded by a nucleic acid that hybridizes to the "MGC4022" nucleic acid or its complement under low stringency conditions,

(x) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,

(xi) "NAP-1 related protein" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NAP-1 related protein", the variant being encoded by a nucleic acid that hybridizes to the "NAP-1 related protein" nucleic acid or its complement under low stringency conditions,

(xii) "Neurocalcin delta" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurocalcin delta", the variant being encoded by a nucleic acid that hybridizes to the "Neurocalcin delta" nucleic acid or its complement under low stringency conditions,

(xiii) "REST corepressor" (SEQ ID No:239) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "REST corepressor", the variant being encoded by a nucleic acid that hybridizes to the "REST corepressor" nucleic acid or its complement under low stringency conditions,

(xiv) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions,

(xv) "S-100 beta" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions,

(xvi) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the signalling activity (regulation of transcription).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:

expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the APP-C99 complex obtainable by a process according to any of No. 9 - 11.
13. Protein of the APP-C99 complex selected from
  - (i) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,
  - (ii) "KIAA1949" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1949", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
  - (iii) "MGC4022" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4022", the variant being encoded by a nucleic acid that hybridizes to the "MGC4022" nucleic acid or its complement under low stringency conditions, and
  - (iv) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
14. Nucleic acid encoding a protein according to No. 13.
15. Construct, preferably a vector construct, comprising:

- (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
- (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b) or
- (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container:

- (a) the complex of any of No. 1 - 8 and/or the proteins of No. 13 and/or
- (b) an antibody according to No. 17 and/or
- (c) a nucleic acid encoding a protein of the complex of any of No. 1 - 8 and/or a protein of No. 13 and/or
- (d) cells expressing the complex of any of No. 1 - 8 and/or a protein of No. 13 and, optionally,
- (e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.
20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.
21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.
22. A process for modifying a physiological substrate of the complex comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.
23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
- (i) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,
  - (ii) "KIAA1949" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1949", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
  - (iii) "MGC4022" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4022", the variant being encoded by a nucleic acid that hybridizes to the "MGC4022" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to a complex of anyone of No. 1 - 8 and/or any of the following the proteins:

- (i) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,
- (ii) "KIAA1949" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1949", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (iii) "MGC4022" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4022", the variant being encoded by a nucleic acid that hybridizes to the "MGC4022" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions, comprising the steps of:
  - (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and
  - (b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:

- (a) exposing said complex, or a cell or organism containing APP-C99 complex to one or more candidate molecules; and
- (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the

complex and/or the abundance and/or activity of a protein or protein complex regulated by the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether (i) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APP-C99" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP-C99", the variant being encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Delta-like homologue" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-like

homologue", the variant being encoded by a nucleic acid that hybridizes to the "Delta-like homologue" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

(v) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or

(vi) "Integral membrane transporter protein" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane transporter protein", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane transporter protein" nucleic acid or its complement under low stringency conditions, and/or

(vii) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions, and/or

(viii) "KIAA1949" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1949", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions, and/or

(ix) "MGC4022" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4022", the variant being encoded by a nucleic acid that hybridizes to the "MGC4022" nucleic acid or its complement under low stringency conditions, and/or

(x) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions, and/or

(xi) "NAP-1 related protein" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NAP-1

related protein", the variant being encoded by a nucleic acid that hybridizes to the "NAP-1 related protein" nucleic acid or its complement under low stringency conditions, and/or

(xii) "Neurocalcin delta" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurocalcin delta", the variant being encoded by a nucleic acid that hybridizes to the "Neurocalcin delta" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "REST corepressor" (SEQ ID No:239) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "REST corepressor", the variant being encoded by a nucleic acid that hybridizes to the "REST corepressor" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions, and/or

(xv) "S-100 beta" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity,

composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether (i) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being

encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APP-C99" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP-C99", the variant being encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Delta-like homologue" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-like homologue", the variant being encoded by a nucleic acid that hybridizes to the "Delta-like homologue" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

(v) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or

(vi) "Integral membrane transporter protein" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane transporter protein", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane transporter protein" nucleic acid or its complement under low stringency conditions, and/or

(vii) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions, and/or

(viii) "KIAA1949" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1949", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions, and/or

(ix) "MGC4022" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4022",

the variant being encoded by a nucleic acid that hybridizes to the "MGC4022" nucleic acid or its complement under low stringency conditions, and/or

(x) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions, and/or

(xi) "NAP-1 related protein" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NAP-1 related protein", the variant being encoded by a nucleic acid that hybridizes to the "NAP-1 related protein" nucleic acid or its complement under low stringency conditions, and/or

(xii) "Neurocalcin delta" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurocalcin delta", the variant being encoded by a nucleic acid that hybridizes to the "Neurocalcin delta" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "REST corepressor" (SEQ ID No:239) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "REST corepressor", the variant being encoded by a nucleic acid that hybridizes to the "REST corepressor" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions, and/or

(xv) "S-100 beta" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as

neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the signalling activity (regulation of transcription) of, or protein composition of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins:

- (i) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (ii) "APP-C99" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP-C99", the variant being encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iii) "Delta-like homologue" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-like homologue", the variant being encoded by a nucleic acid that hybridizes to the "Delta-like homologue" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(v) "Fe65L1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65L1", the variant being encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(vi) "Integral membrane transporter protein" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Integral membrane transporter protein", the variant being encoded by a nucleic acid that hybridizes to the "Integral membrane transporter protein" nucleic acid or its complement under low stringency conditions,

(vii) "KIAA1102" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1102", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,

(viii) "KIAA1949" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA1949", the variant being encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,

(ix) "MGC4022" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4022", the variant being encoded by a nucleic acid that hybridizes to the "MGC4022" nucleic acid or its complement under low stringency conditions,

(x) "MGC5442" (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC5442", the variant being encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,

(xi) "NAP-1 related protein" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "NAP-1 related protein", the variant being encoded by a nucleic acid that hybridizes to the "NAP-1 related protein" nucleic acid or its complement under low stringency conditions,

(xii) "Neurocalcin delta" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurocalcin delta", the variant being encoded by a nucleic acid that hybridizes to the "Neurocalcin delta" nucleic acid or its complement under low stringency conditions,

(xiii) "REST corepressor" (SEQ ID No:239) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "REST corepressor", the variant being encoded by a nucleic acid that hybridizes to the "REST corepressor" nucleic acid or its complement under low stringency conditions,

(xiv) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions,

(xv) "S-100 beta" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions, and/or (xvi) "X11beta" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "X11beta", the variant being encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

The invention further relates to the Tau complex:

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "14-3-3 protein zeta/delta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein zeta/delta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein zeta/delta" nucleic acid or its complement under low stringency conditions,
    - (ii) "Actin" (SEQ ID No:240) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Actin", the variant being encoded by a nucleic acid that hybridizes to the "Actin" nucleic acid or its complement under low stringency conditions,

- (iii) "Alpha tubulin" (SEQ ID No:241) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha tubulin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha tubulin" nucleic acid or its complement under low stringency conditions,
- (iv) "Beta tubulin" (SEQ ID No:242) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Beta tubulin", the variant being encoded by a nucleic acid that hybridizes to the "Beta tubulin" nucleic acid or its complement under low stringency conditions,
- (v) "PPP2CA (PP2A, catalytic subunit, alpha)" (SEQ ID No:247) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2CA (PP2A, catalytic subunit, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2CA (PP2A, catalytic subunit, alpha)" nucleic acid or its complement under low stringency conditions,
- (vi) "PPP2CB (PP2A, catalytic subunit, beta)" (SEQ ID No:248) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2CB (PP2A, catalytic subunit, beta)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2CB (PP2A, catalytic subunit, beta)" nucleic acid or its complement under low stringency conditions,
- (vii) "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)" (SEQ ID No:249) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)" nucleic acid or its complement under low stringency conditions,
- (viii) "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)" nucleic acid or its complement under low stringency conditions, and
- (ix) "Tau" (SEQ ID No:250) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Tau", the variant being encoded by a nucleic acid that hybridizes to the "Tau" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

- (i) "Deoxyhypusine synthase " (SEQ ID No:243) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Deoxyhypusine synthase ", the variant being encoded by a nucleic acid that hybridizes to the "Deoxyhypusine synthase " nucleic acid or its complement under low stringency conditions,
- (ii) "Dynactin 2 " (SEQ ID No:244) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynactin 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Dynactin 2 " nucleic acid or its complement under low stringency conditions,
- (iii) "MEP50" (SEQ ID No:245) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEP50", the variant being encoded by a nucleic acid that hybridizes to the "MEP50" nucleic acid or its complement under low stringency conditions,
- (iv) "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1" (SEQ ID No:246) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1", the variant being encoded by a nucleic acid that hybridizes to the "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1" nucleic acid or its complement under low stringency conditions, and
- (v) "S-100 beta " (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta ", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta " nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. The protein complex according to No. 1 wherein the first protein is the protein "Tau" (SEQ ID No:250), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Tau", the variant being encoded by a nucleic acid that hybridizes to the "Tau" nucleic acid under low stringency conditions.

3. The protein complex according to No. 1 comprising the following proteins:

- (i) "14-3-3 protein zeta/delta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein zeta/delta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein zeta/delta" nucleic acid or its complement under low stringency conditions,
- (ii) "Actin" (SEQ ID No:240) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Actin", the variant being encoded by a nucleic acid that hybridizes to the "Actin" nucleic acid or its complement under low stringency conditions,
- (iii) "Alpha tubulin" (SEQ ID No:241) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha tubulin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha tubulin" nucleic acid or its complement under low stringency conditions,
- (iv) "Beta tubulin" (SEQ ID No:242) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Beta tubulin", the variant being encoded by a nucleic acid that hybridizes to the "Beta tubulin" nucleic acid or its complement under low stringency conditions,
- (v) "Deoxyhypusine synthase " (SEQ ID No:243) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Deoxyhypusine synthase ", the variant being encoded by a nucleic acid that hybridizes to the "Deoxyhypusine synthase " nucleic acid or its complement under low stringency conditions,
- (vi) "Dynactin 2 " (SEQ ID No:244) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynactin 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Dynactin 2 " nucleic acid or its complement under low stringency conditions,
- (vii) "MEP50" (SEQ ID No:245) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEP50", the variant

being encoded by a nucleic acid that hybridizes to the "MEP50" nucleic acid or its complement under low stringency conditions,

(viii) "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1" (SEQ ID No:246) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1", the variant being encoded by a nucleic acid that hybridizes to the "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1" nucleic acid or its complement under low stringency conditions,

(ix) "PPP2CA (PP2A, catalytic subunit, alpha)" (SEQ ID No:247) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2CA (PP2A, catalytic subunit, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2CA (PP2A, catalytic subunit, alpha)" nucleic acid or its complement under low stringency conditions,

(x) "PPP2CB (PP2A, catalytic subunit, beta)" (SEQ ID No:248) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2CB (PP2A, catalytic subunit, beta)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2CB (PP2A, catalytic subunit, beta)" nucleic acid or its complement under low stringency conditions,

(xi) "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)" (SEQ ID No:249) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)" nucleic acid or its complement under low stringency conditions,

(xii) "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)" nucleic acid or its complement under low stringency conditions,

(xiii) "S-100 beta " (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta ", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta " nucleic acid or its complement under low stringency conditions, and/or

(xiv) "Tau" (SEQ ID No:250) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Tau", the variant being encoded by a nucleic acid that hybridizes to the "Tau" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising at least 10 but no more than 13 of the following proteins:

- (i) "14-3-3 protein zeta/delta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein zeta/delta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein zeta/delta" nucleic acid or its complement under low stringency conditions,
- (ii) "Actin" (SEQ ID No:240) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Actin", the variant being encoded by a nucleic acid that hybridizes to the "Actin" nucleic acid or its complement under low stringency conditions,
- (iii) "Alpha tubulin" (SEQ ID No:241) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha tubulin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha tubulin" nucleic acid or its complement under low stringency conditions,
- (iv) "Beta tubulin" (SEQ ID No:242) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Beta tubulin", the variant being encoded by a nucleic acid that hybridizes to the "Beta tubulin" nucleic acid or its complement under low stringency conditions,
- (v) "Deoxyhypusine synthase " (SEQ ID No:243) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Deoxyhypusine synthase ", the variant being encoded by a nucleic acid that hybridizes to the "Deoxyhypusine synthase " nucleic acid or its complement under low stringency conditions,
- (vi) "Dynactin 2 " (SEQ ID No:244) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynactin 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Dynactin 2 " nucleic acid or its complement under low stringency conditions,
- (vii) "MEP50" (SEQ ID No:245) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEP50", the variant

being encoded by a nucleic acid that hybridizes to the "MEP50" nucleic acid or its complement under low stringency conditions,

(viii) "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1" (SEQ ID No:246) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1", the variant being encoded by a nucleic acid that hybridizes to the "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1" nucleic acid or its complement under low stringency conditions,

(ix) "PPP2CA (PP2A, catalytic subunit, alpha)" (SEQ ID No:247) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2CA (PP2A, catalytic subunit, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2CA (PP2A, catalytic subunit, alpha)" nucleic acid or its complement under low stringency conditions,

(x) "PPP2CB (PP2A, catalytic subunit, beta)" (SEQ ID No:248) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2CB (PP2A, catalytic subunit, beta)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2CB (PP2A, catalytic subunit, beta)" nucleic acid or its complement under low stringency conditions,

(xi) "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)" (SEQ ID No:249) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)" nucleic acid or its complement under low stringency conditions,

(xii) "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)" nucleic acid or its complement under low stringency conditions,

(xiii) "S-100 beta " (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta ", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta " nucleic acid or its complement under low stringency conditions,

(xiv) "Tau" (SEQ ID No:250) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Tau", the variant being encoded by a nucleic acid that hybridizes to the "Tau" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the regulation of microtubules and vesicle transport along microtubules.

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:  
expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Tau complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the Tau complex selected from

(i) "MEP50" (SEQ ID No:245) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEP50", the variant being encoded by a nucleic acid that hybridizes to the "MEP50" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising:

(a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or

(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b) or

(c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or

functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container:

(a) the complex of any of No. 1 - 8 and/or the proteins of No. 13 and/or

(b) an antibody according to No. 17 and/or

(c) a nucleic acid encoding a protein of the complex of any of No. 1 - 8 and/or a protein of No. 13 and/or

(d) cells expressing the complex of any of No. 1 - 8 and/or a protein of No. 13 and, optionally,

(e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for modifying a physiological substrate of the complex comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "MEP50" (SEQ ID No:245) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEP50", the variant being encoded by a nucleic acid that hybridizes to the "MEP50" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to a complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "MEP50" (SEQ ID No:245) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEP50", the variant being encoded by a nucleic acid that hybridizes to the "MEP50" nucleic acid or its complement under low stringency conditions, comprising the steps of:

(a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:

(a) exposing said complex, or a cell or organism containing Tau complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex regulated by the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a

protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether (i) "14-3-3 protein zeta/delta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein zeta/delta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein zeta/delta" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Actin" (SEQ ID No:240) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Actin", the variant being encoded by a nucleic acid that hybridizes to the "Actin" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Alpha tubulin" (SEQ ID No:241) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha tubulin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha tubulin" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Beta tubulin" (SEQ ID No:242) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Beta

tubulin", the variant being encoded by a nucleic acid that hybridizes to the "Beta tubulin" nucleic acid or its complement under low stringency conditions, and/or

(v) "Deoxyhypusine synthase " (SEQ ID No:243) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Deoxyhypusine synthase ", the variant being encoded by a nucleic acid that hybridizes to the "Deoxyhypusine synthase " nucleic acid or its complement under low stringency conditions, and/or

(vi) "Dynactin 2 " (SEQ ID No:244) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynactin 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Dynactin 2 " nucleic acid or its complement under low stringency conditions, and/or

(vii) "MEP50" (SEQ ID No:245) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEP50", the variant being encoded by a nucleic acid that hybridizes to the "MEP50" nucleic acid or its complement under low stringency conditions, and/or

(viii) "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1" (SEQ ID No:246) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1", the variant being encoded by a nucleic acid that hybridizes to the "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1" nucleic acid or its complement under low stringency conditions, and/or

(ix) "PPP2CA (PP2A, catalytic subunit, alpha)" (SEQ ID No:247) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2CA (PP2A, catalytic subunit, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2CA (PP2A, catalytic subunit, alpha)" nucleic acid or its complement under low stringency conditions, and/or

(x) "PPP2CB (PP2A, catalytic subunit, beta)" (SEQ ID No:248) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2CB (PP2A, catalytic subunit, beta)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2CB (PP2A, catalytic subunit, beta)" nucleic acid or its complement under low stringency conditions, and/or

(xi) "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)" (SEQ ID No:249) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2R1A (PP2A, 65 KDA regulatory subunit A,

alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)" nucleic acid or its complement under low stringency conditions, and/or

(xii) "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "S-100 beta " (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta ", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta " nucleic acid or its complement under low stringency conditions, and/or

(xiv) "Tau" (SEQ ID No:250) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Tau", the variant being encoded by a nucleic acid that hybridizes to the "Tau" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or

disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether  
(i) "14-3-3 protein zeta/delta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein zeta/delta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein zeta/delta" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Actin" (SEQ ID No:240) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Actin", the variant being

encoded by a nucleic acid that hybridizes to the "Actin" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Alpha tubulin" (SEQ ID No:241) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha tubulin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha tubulin" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Beta tubulin" (SEQ ID No:242) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Beta tubulin", the variant being encoded by a nucleic acid that hybridizes to the "Beta tubulin" nucleic acid or its complement under low stringency conditions, and/or

(v) "Deoxyhypusine synthase " (SEQ ID No:243) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Deoxyhypusine synthase ", the variant being encoded by a nucleic acid that hybridizes to the "Deoxyhypusine synthase " nucleic acid or its complement under low stringency conditions, and/or

(vi) "Dynactin 2 " (SEQ ID No:244) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynactin 2 ", the variant being encoded by a nucleic acid that hybridizes to the "Dynactin 2 " nucleic acid or its complement under low stringency conditions, and/or

(vii) "MEP50" (SEQ ID No:245) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEP50", the variant being encoded by a nucleic acid that hybridizes to the "MEP50" nucleic acid or its complement under low stringency conditions, and/or

(viii) "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1" (SEQ ID No:246) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1", the variant being encoded by a nucleic acid that hybridizes to the "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1" nucleic acid or its complement under low stringency conditions, and/or

(ix) "PPP2CA (PP2A, catalytic subunit, alpha)" (SEQ ID No:247) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2CA (PP2A, catalytic subunit, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2CA (PP2A, catalytic subunit, alpha)" nucleic acid or its complement under low stringency conditions, and/or

- (x) "PPP2CB (PP2A, catalytic subunit, beta)" (SEQ ID No:248) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2CB (PP2A, catalytic subunit, beta)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2CB (PP2A, catalytic subunit, beta)" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)" (SEQ ID No:249) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "S-100 beta " (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta ", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta " nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "Tau" (SEQ ID No:250) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Tau", the variant being encoded by a nucleic acid that hybridizes to the "Tau" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such

treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the regulation of microtubules of, or protein composition of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins:

- (i) "14-3-3 protein zeta/delta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "14-3-3 protein zeta/delta", the variant being encoded by a nucleic acid that hybridizes to the "14-3-3 protein zeta/delta" nucleic acid or its complement under low stringency conditions,
- (ii) "Actin" (SEQ ID No:240) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Actin", the variant being encoded by a nucleic acid that hybridizes to the "Actin" nucleic acid or its complement under low stringency conditions,
- (iii) "Alpha tubulin" (SEQ ID No:241) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Alpha tubulin", the variant being encoded by a nucleic acid that hybridizes to the "Alpha tubulin" nucleic acid or its complement under low stringency conditions,
- (iv) "Beta tubulin" (SEQ ID No:242) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Beta tubulin", the variant being encoded by a nucleic acid that hybridizes to the "Beta tubulin" nucleic acid or its complement under low stringency conditions,
- (v) "Deoxyhypusine synthase " (SEQ ID No:243) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Deoxyhypusine synthase ", the variant being encoded by a nucleic acid that hybridizes to the "Deoxyhypusine synthase " nucleic acid or its complement under low stringency conditions,
- (vi) "Dynactin 2 " (SEQ ID No:244) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Dynactin 2 ",

the variant being encoded by a nucleic acid that hybridizes to the "Dynactin 2 " nucleic acid or its complement under low stringency conditions,

(vii) "MEP50" (SEQ ID No:245) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MEP50", the variant being encoded by a nucleic acid that hybridizes to the "MEP50" nucleic acid or its complement under low stringency conditions,

(viii) "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1" (SEQ ID No:246) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1", the variant being encoded by a nucleic acid that hybridizes to the "Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1" nucleic acid or its complement under low stringency conditions,

(ix) "PPP2CA (PP2A, catalytic subunit, alpha)" (SEQ ID No:247) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2CA (PP2A, catalytic subunit, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2CA (PP2A, catalytic subunit, alpha)" nucleic acid or its complement under low stringency conditions,

(x) "PPP2CB (PP2A, catalytic subunit, beta)" (SEQ ID No:248) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2CB (PP2A, catalytic subunit, beta)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2CB (PP2A, catalytic subunit, beta)" nucleic acid or its complement under low stringency conditions,

(xi) "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)" (SEQ ID No:249) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)" nucleic acid or its complement under low stringency conditions,

(xii) "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)", the variant being encoded by a nucleic acid that hybridizes to the "PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)" nucleic acid or its complement under low stringency conditions,

(xiii) "S-100 beta " (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 beta ", the variant being encoded by a nucleic acid that hybridizes to the "S-100 beta " nucleic acid or its complement under low stringency conditions, and/or(xiv) "Tau" (SEQ ID No:250) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Tau", the variant being encoded by a nucleic acid that hybridizes to the "Tau" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

The invention further relates to the BACE1 D215N complex:

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "BACE1 D215N" (SEQ ID No:266) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BACE1 D215N", the variant being encoded by a nucleic acid that hybridizes to the "BACE1 D215N" nucleic acid or its complement under low stringency conditions, and
    - (ii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one second protein, which second protein is selected from the group consisting of:
    - (i) "ADP-ribosylation factor 4" (SEQ ID No:251) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADP-ribosylation factor 4", the variant being encoded by a nucleic acid that hybridizes to the "ADP-ribosylation factor 4" nucleic acid or its complement under low stringency conditions,
    - (ii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being

encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "Acetylcholine receptor beta-4" (SEQ ID No:252) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Acetylcholine receptor beta-4", the variant being encoded by a nucleic acid that hybridizes to the "Acetylcholine receptor beta-4" nucleic acid or its complement under low stringency conditions,

(iv) "Calcium binding protein Cab45" (SEQ ID No:253) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calcium binding protein Cab45", the variant being encoded by a nucleic acid that hybridizes to the "Calcium binding protein Cab45" nucleic acid or its complement under low stringency conditions,

(v) "DNAJC3" (SEQ ID No:254) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DNAJC3", the variant being encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions,

(vi) "Delta-like homologue" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-like homologue", the variant being encoded by a nucleic acid that hybridizes to the "Delta-like homologue" nucleic acid or its complement under low stringency conditions,

(vii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(viii) "KIAA0747" (SEQ ID No:255) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0747", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0747" nucleic acid or its complement under low stringency conditions,

(ix) "MGC4248" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248" nucleic acid or its complement under low stringency conditions,

(x) "Neural cell adhesion molecule L1" (SEQ ID No:256) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a

variant of "Neural cell adhesion molecule L1 ", the variant being encoded by a nucleic acid that hybridizes to the "Neural cell adhesion molecule L1 " nucleic acid or its complement under low stringency conditions,

(xi) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xii) "Protein amplified in osteosarcoma (OS-9)" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein amplified in osteosarcoma (OS-9)", the variant being encoded by a nucleic acid that hybridizes to the "Protein amplified in osteosarcoma (OS-9)" nucleic acid or its complement under low stringency conditions,

(xiii) "Protocadherin beta 10" (SEQ ID No:257) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 10", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 10" nucleic acid or its complement under low stringency conditions,

(xiv) "Protocadherin beta 14" (SEQ ID No:258) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 14", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 14" nucleic acid or its complement under low stringency conditions,

(xv) "Protocadherin beta 7" (SEQ ID No:259) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 7", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7" nucleic acid or its complement under low stringency conditions,

(xvi) "Protocadherin gamma C3" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin gamma C3", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3" nucleic acid or its complement under low stringency conditions,

(xvii) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100

alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions,

(xviii) "SEL-1 homologue" (SEQ ID No:260) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SEL-1 homologue", the variant being encoded by a nucleic acid that hybridizes to the "SEL-1 homologue" nucleic acid or its complement under low stringency conditions,

(xix) "Seipin" (SEQ ID No:261) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Seipin", the variant being encoded by a nucleic acid that hybridizes to the "Seipin" nucleic acid or its complement under low stringency conditions, and

(xx) "Stromal cell-derived factor 2-like 1" (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stromal cell-derived factor 2-like 1", the variant being encoded by a nucleic acid that hybridizes to the "Stromal cell-derived factor 2-like 1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. The protein complex according to No. 1 wherein the first protein is the protein "BACE1 D215N" (SEQ ID No:266), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BACE1 D215N", the variant being encoded by a nucleic acid that hybridizes to the "BACE1 D215N" under low stringency conditions.

3. The protein complex according to No. 1 comprising the following proteins:

(i) "ADP-ribosylation factor 4" (SEQ ID No:251) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADP-ribosylation factor 4", the variant being encoded by a nucleic acid that hybridizes to the

"ADP-ribosylation factor 4" nucleic acid or its complement under low stringency conditions,

(ii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "Acetylcholine receptor beta-4" (SEQ ID No:252) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Acetylcholine receptor beta-4", the variant being encoded by a nucleic acid that hybridizes to the "Acetylcholine receptor beta-4" nucleic acid or its complement under low stringency conditions,

(iv) "BACE1 D215N" (SEQ ID No:266) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BACE1 D215N", the variant being encoded by a nucleic acid that hybridizes to the "BACE1 D215N" nucleic acid or its complement under low stringency conditions,

(v) "Calcium binding protein Cab45" (SEQ ID No:253) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calcium binding protein Cab45", the variant being encoded by a nucleic acid that hybridizes to the "Calcium binding protein Cab45" nucleic acid or its complement under low stringency conditions,

(vi) "DNAJC3" (SEQ ID No:254) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DNAJC3", the variant being encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions,

(vii) "Delta-like homologue" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-like homologue", the variant being encoded by a nucleic acid that hybridizes to the "Delta-like homologue" nucleic acid or its complement under low stringency conditions,

(viii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(ix) "KIAA0747" (SEQ ID No:255) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0747",

the variant being encoded by a nucleic acid that hybridizes to the "KIAA0747" nucleic acid or its complement under low stringency conditions,

(x) "MGC4248" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248" nucleic acid or its complement under low stringency conditions,

(xi) "Neural cell adhesion molecule L1 " (SEQ ID No:256) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neural cell adhesion molecule L1 ", the variant being encoded by a nucleic acid that hybridizes to the "Neural cell adhesion molecule L1 " nucleic acid or its complement under low stringency conditions,

(xii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xiii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(xiv) "Protein amplified in osteosarcoma (OS-9)" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein amplified in osteosarcoma (OS-9)", the variant being encoded by a nucleic acid that hybridizes to the "Protein amplified in osteosarcoma (OS-9)" nucleic acid or its complement under low stringency conditions,

(xv) "Protocadherin beta 10" (SEQ ID No:257) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 10", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 10" nucleic acid or its complement under low stringency conditions,

(xvi) "Protocadherin beta 14" (SEQ ID No:258) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 14", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 14" nucleic acid or its complement under low stringency conditions,

(xvii) "Protocadherin beta 7" (SEQ ID No:259) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 7", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7" nucleic acid or its complement under low stringency conditions,

(xviii) "Protocadherin gamma C3" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin gamma C3", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3" nucleic acid or its complement under low stringency conditions,

(xix) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions,

(xx) "SEL-1 homologue" (SEQ ID No:260) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SEL-1 homologue", the variant being encoded by a nucleic acid that hybridizes to the "SEL-1 homologue" nucleic acid or its complement under low stringency conditions,

(xxi) "Seipin" (SEQ ID No:261) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Seipin", the variant being encoded by a nucleic acid that hybridizes to the "Seipin" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "Stromal cell-derived factor 2-like 1" (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stromal cell-derived factor 2-like 1", the variant being encoded by a nucleic acid that hybridizes to the "Stromal cell-derived factor 2-like 1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising at least 3 but no more than 21 of the following proteins:

(i) "ADP-ribosylation factor 4" (SEQ ID No:251) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADP-ribosylation factor 4", the variant being encoded by a nucleic acid that hybridizes to the "ADP-ribosylation factor 4" nucleic acid or its complement under low stringency conditions,

- (ii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "Acetylcholine receptor beta-4" (SEQ ID No:252) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Acetylcholine receptor beta-4", the variant being encoded by a nucleic acid that hybridizes to the "Acetylcholine receptor beta-4" nucleic acid or its complement under low stringency conditions,
- (iv) "BACE1 D215N" (SEQ ID No:266) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BACE1 D215N", the variant being encoded by a nucleic acid that hybridizes to the "BACE1 D215N" nucleic acid or its complement under low stringency conditions,
- (v) "Calcium binding protein Cab45" (SEQ ID No:253) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calcium binding protein Cab45", the variant being encoded by a nucleic acid that hybridizes to the "Calcium binding protein Cab45" nucleic acid or its complement under low stringency conditions,
- (vi) "DNAJC3" (SEQ ID No:254) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DNAJC3", the variant being encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions,
- (vii) "Delta-like homologue" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-like homologue", the variant being encoded by a nucleic acid that hybridizes to the "Delta-like homologue" nucleic acid or its complement under low stringency conditions,
- (viii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (ix) "KIAA0747" (SEQ ID No:255) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0747", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0747" nucleic acid or its complement under low stringency conditions,

- (x) "MGC4248" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248" nucleic acid or its complement under low stringency conditions,
- (xi) "Neural cell adhesion molecule L1 " (SEQ ID No:256) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neural cell adhesion molecule L1 ", the variant being encoded by a nucleic acid that hybridizes to the "Neural cell adhesion molecule L1 " nucleic acid or its complement under low stringency conditions,
- (xii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xiii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (xiv) "Protein amplified in osteosarcoma (OS-9)" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein amplified in osteosarcoma (OS-9)", the variant being encoded by a nucleic acid that hybridizes to the "Protein amplified in osteosarcoma (OS-9)" nucleic acid or its complement under low stringency conditions,
- (xv) "Protocadherin beta 10" (SEQ ID No:257) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 10", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 10" nucleic acid or its complement under low stringency conditions,
- (xvi) "Protocadherin beta 14" (SEQ ID No:258) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 14", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 14" nucleic acid or its complement under low stringency conditions,
- (xvii) "Protocadherin beta 7" (SEQ ID No:259) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Protocadherin beta 7", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7" nucleic acid or its complement under low stringency conditions, (xviii) "Protocadherin gamma C3" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin gamma C3", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3" nucleic acid or its complement under low stringency conditions,

(xix) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions,

(xx) "SEL-1 homologue" (SEQ ID No:260) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SEL-1 homologue", the variant being encoded by a nucleic acid that hybridizes to the "SEL-1 homologue" nucleic acid or its complement under low stringency conditions,

(xxi) "Seipin" (SEQ ID No:261) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Seipin", the variant being encoded by a nucleic acid that hybridizes to the "Seipin" nucleic acid or its complement under low stringency conditions,

(xxii) "Stromal cell-derived factor 2-like 1" (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stromal cell-derived factor 2-like 1", the variant being encoded by a nucleic acid that hybridizes to the "Stromal cell-derived factor 2-like 1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the beta-secretase activity.

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:

expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the BACE1 D215N complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the BACE1 D215N complex selected from

(i) "MGC4248" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248" nucleic acid or its complement under low stringency conditions, and

(ii) "Protocadherin beta 7" (SEQ ID No:259) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 7", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate

for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising:

- (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
- (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b) or
- (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container:

(a) the complex of any of No. 1 – 8 and/or the proteins of No. 13 and/or

(b) an antibody according to No. 17 and/or

(c) a nucleic acid encoding a protein of the complex of any of No. 1 – 8 and/or a protein of No. 13 and/or

(d) cells expressing the complex of any of No. 1 – 8 and/or a protein of No. 13 and, optionally,

(e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for modifying a physiological substrate of the complex comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "MGC4248" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Protocadherin beta 7" (SEQ ID No:259) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 7", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to a complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "MGC4248" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Protocadherin beta 7" (SEQ ID No:259) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 7", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7" nucleic acid or its complement under low stringency conditions, comprising the steps of:

(a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:

(a) exposing said complex, or a cell or organism containing BACE1 D215N complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex regulated by the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a

gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether (i) "ADP-ribosylation factor 4" (SEQ ID No:251) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADP-ribosylation factor 4", the variant being encoded by a nucleic acid that hybridizes to the "ADP-ribosylation factor 4" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Acetylcholine receptor beta-4" (SEQ ID No:252) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Acetylcholine receptor beta-4", the variant being encoded by a nucleic acid that hybridizes to the "Acetylcholine receptor beta-4" nucleic acid or its complement under low stringency conditions, and/or

(iv) "BACE1 D215N" (SEQ ID No:266) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BACE1

D215N", the variant being encoded by a nucleic acid that hybridizes to the "BACE1 D215N" nucleic acid or its complement under low stringency conditions, and/or

(v) "Calcium binding protein Cab45" (SEQ ID No:253) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calcium binding protein Cab45", the variant being encoded by a nucleic acid that hybridizes to the "Calcium binding protein Cab45" nucleic acid or its complement under low stringency conditions, and/or

(vi) "DNAJC3" (SEQ ID No:254) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DNAJC3", the variant being encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions, and/or

(vii) "Delta-like homologue" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-like homologue", the variant being encoded by a nucleic acid that hybridizes to the "Delta-like homologue" nucleic acid or its complement under low stringency conditions, and/or

(viii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

(ix) "KIAA0747" (SEQ ID No:255) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0747", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0747" nucleic acid or its complement under low stringency conditions, and/or

(x) "MGC4248" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248" nucleic acid or its complement under low stringency conditions, and/or

(xi) "Neural cell adhesion molecule L1 " (SEQ ID No:256) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neural cell adhesion molecule L1 ", the variant being encoded by a nucleic acid that hybridizes to the "Neural cell adhesion molecule L1 " nucleic acid or its complement under low stringency conditions, and/or

(xii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of

"Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "Protein amplified in osteosarcoma (OS-9)" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein amplified in osteosarcoma (OS-9)", the variant being encoded by a nucleic acid that hybridizes to the "Protein amplified in osteosarcoma (OS-9)" nucleic acid or its complement under low stringency conditions, and/or

(xv) "Protocadherin beta 10" (SEQ ID No:257) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 10", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 10" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "Protocadherin beta 14" (SEQ ID No:258) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 14", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 14" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "Protocadherin beta 7" (SEQ ID No:259) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 7", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "Protocadherin gamma C3" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin gamma C3", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3" nucleic acid or its complement under low stringency conditions, and/or

(xix) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100

alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions, and/or  
 (xx) "SEL-1 homologue" (SEQ ID No:260) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SEL-1 homologue", the variant being encoded by a nucleic acid that hybridizes to the "SEL-1 homologue" nucleic acid or its complement under low stringency conditions, and/or  
 (xxi) "Seipin" (SEQ ID No:261) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Seipin", the variant being encoded by a nucleic acid that hybridizes to the "Seipin" nucleic acid or its complement under low stringency conditions, and/or  
 (xxii) "Stromal cell-derived factor 2-like 1" (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stromal cell-derived factor 2-like 1", the variant being encoded by a nucleic acid that hybridizes to the "Stromal cell-derived factor 2-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising

determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether (i) "ADP-ribosylation factor 4" (SEQ ID No:251) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADP-ribosylation factor 4", the variant being encoded by a nucleic acid that hybridizes to the "ADP-ribosylation factor 4" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

- (iii) "Acetylcholine receptor beta-4" (SEQ ID No:252) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Acetylcholine receptor beta-4", the variant being encoded by a nucleic acid that hybridizes to the "Acetylcholine receptor beta-4" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "BACE1 D215N" (SEQ ID No:266) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BACE1 D215N", the variant being encoded by a nucleic acid that hybridizes to the "BACE1 D215N" nucleic acid or its complement under low stringency conditions, and/or
- (v) "Calcium binding protein Cab45" (SEQ ID No:253) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calcium binding protein Cab45", the variant being encoded by a nucleic acid that hybridizes to the "Calcium binding protein Cab45" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "DNAJC3" (SEQ ID No:254) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DNAJC3", the variant being encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "Delta-like homologue" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-like homologue", the variant being encoded by a nucleic acid that hybridizes to the "Delta-like homologue" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "KIAA0747" (SEQ ID No:255) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0747", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0747" nucleic acid or its complement under low stringency conditions, and/or
- (x) "MGC4248" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248" nucleic acid or its complement under low stringency conditions, and/or

- (xi) "Neural cell adhesion molecule L1 " (SEQ ID No:256) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neural cell adhesion molecule L1 ", the variant being encoded by a nucleic acid that hybridizes to the "Neural cell adhesion molecule L1 " nucleic acid or its complement under low stringency conditions, and/or
- (xii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "Protein amplified in osteosarcoma (OS-9)" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein amplified in osteosarcoma (OS-9)", the variant being encoded by a nucleic acid that hybridizes to the "Protein amplified in osteosarcoma (OS-9)" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "Protocadherin beta 10" (SEQ ID No:257) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 10", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 10" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "Protocadherin beta 14" (SEQ ID No:258) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 14", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 14" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "Protocadherin beta 7" (SEQ ID No:259) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 7", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "Protocadherin gamma C3" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin gamma C3", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3" nucleic acid or its complement under low stringency conditions, and/or

(xix) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions, and/or

(xx) "SEL-1 homologue" (SEQ ID No:260) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SEL-1 homologue", the variant being encoded by a nucleic acid that hybridizes to the "SEL-1 homologue" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "Seipin" (SEQ ID No:261) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Seipin", the variant being encoded by a nucleic acid that hybridizes to the "Seipin" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "Stromal cell-derived factor 2-like 1" (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Stromal cell-derived factor 2-like 1", the variant being encoded by a nucleic acid that hybridizes to the "Stromal cell-derived factor 2-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the beta-secretase activity of, or protein composition of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.
44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.
45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins:
- (i) "ADP-ribosylation factor 4" (SEQ ID No:251) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "ADP-ribosylation factor 4", the variant being encoded by a nucleic acid that hybridizes to the "ADP-ribosylation factor 4" nucleic acid or its complement under low stringency conditions,
  - (ii) "APP" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "APP", the variant being encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
  - (iii) "Acetylcholine receptor beta-4" (SEQ ID No:252) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Acetylcholine receptor beta-4", the variant being encoded by a nucleic acid that hybridizes to the "Acetylcholine receptor beta-4" nucleic acid or its complement under low stringency conditions,
  - (iv) "BACE1 D215N" (SEQ ID No:266) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "BACE1 D215N", the variant being encoded by a nucleic acid that hybridizes to the "BACE1 D215N" nucleic acid or its complement under low stringency conditions,
  - (v) "Calcium binding protein Cab45" (SEQ ID No:253) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calcium binding protein Cab45", the variant being encoded by a nucleic acid that hybridizes to the "Calcium binding protein Cab45" nucleic acid or its complement under low stringency conditions,
  - (vi) "DNAJC3" (SEQ ID No:254) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "DNAJC3",

the variant being encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions,

(vii) "Delta-like homologue" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Delta-like homologue", the variant being encoded by a nucleic acid that hybridizes to the "Delta-like homologue" nucleic acid or its complement under low stringency conditions,

(viii) "Fe65" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Fe65", the variant being encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(ix) "KIAA0747" (SEQ ID No:255) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KIAA0747", the variant being encoded by a nucleic acid that hybridizes to the "KIAA0747" nucleic acid or its complement under low stringency conditions,

(x) "MGC4248" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "MGC4248", the variant being encoded by a nucleic acid that hybridizes to the "MGC4248" nucleic acid or its complement under low stringency conditions,

(xi) "Neural cell adhesion molecule L1 " (SEQ ID No:256) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neural cell adhesion molecule L1 ", the variant being encoded by a nucleic acid that hybridizes to the "Neural cell adhesion molecule L1 " nucleic acid or its complement under low stringency conditions,

(xii) "Neurotrypsin" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Neurotrypsin", the variant being encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xiii) "Nicastrin" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Nicastrin", the variant being encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(xiv) "Protein amplified in osteosarcoma (OS-9)" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protein amplified in osteosarcoma (OS-9)", the variant being encoded by a

nucleic acid that hybridizes to the "Protein amplified in osteosarcoma (OS-9)" nucleic acid or its complement under low stringency conditions,

(xv) "Protocadherin beta 10" (SEQ ID No:257) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 10", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 10" nucleic acid or its complement under low stringency conditions,

(xvi) "Protocadherin beta 14" (SEQ ID No:258) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 14", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 14" nucleic acid or its complement under low stringency conditions,

(xvii) "Protocadherin beta 7" (SEQ ID No:259) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin beta 7", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7" nucleic acid or its complement under low stringency conditions,

(xviii) "Protocadherin gamma C3" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Protocadherin gamma C3", the variant being encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3" nucleic acid or its complement under low stringency conditions,

(xix) "S-100 alpha" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "S-100 alpha", the variant being encoded by a nucleic acid that hybridizes to the "S-100 alpha" nucleic acid or its complement under low stringency conditions,

(xx) "SEL-1 homologue" (SEQ ID No:260) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "SEL-1 homologue", the variant being encoded by a nucleic acid that hybridizes to the "SEL-1 homologue" nucleic acid or its complement under low stringency conditions,

(xxi) "Seipin" (SEQ ID No:261) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Seipin", the variant being encoded by a nucleic acid that hybridizes to the "Seipin" nucleic acid or its complement under low stringency conditions, and/or (xxii) "Stromal cell-derived factor 2-like 1" (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active

fragment thereof, or a homologue thereof, or a variant of "Stromal cell-derived factor 2-like 1", the variant being encoded by a nucleic acid that hybridizes to the "Stromal cell-derived factor 2-like 1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

The invention further relates to the Calsenilin complex:

1. A protein complex selected from complex (I) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "Calsenilin" (SEQ ID No:263) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsenilin", the variant being encoded by a nucleic acid that hybridizes to the "Calsenilin" nucleic acid or its complement under low stringency conditions, and

(ii) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

(i) "C21ORF57" (SEQ ID No:262) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "C21ORF57", the variant being encoded by a nucleic acid that hybridizes to the "C21ORF57" nucleic acid or its complement under low stringency conditions,

(ii) "KCNQ2" (SEQ ID No:264) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KCNQ2", the variant being encoded by a nucleic acid that hybridizes to the "KCNQ2" nucleic acid or its complement under low stringency conditions, and

(iii) "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7" (SEQ ID No:265) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7", the variant being encoded by a nucleic acid that

hybridizes to the "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. The protein complex according to No. 1 wherein the first protein is the protein "Calsenilin" (SEQ ID No:263), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsenilin", the variant being encoded by a nucleic acid that hybridizes to the "Calsenilin" under low stringency conditions.

3. The protein complex according to No. 1 comprising the following proteins:

- (i) "C21ORF57" (SEQ ID No:262) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "C21ORF57", the variant being encoded by a nucleic acid that hybridizes to the "C21ORF57" nucleic acid or its complement under low stringency conditions,
- (ii) "Calsenilin" (SEQ ID No:263) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsenilin", the variant being encoded by a nucleic acid that hybridizes to the "Calsenilin" nucleic acid or its complement under low stringency conditions,
- (iii) "KCNQ2" (SEQ ID No:264) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KCNQ2", the variant being encoded by a nucleic acid that hybridizes to the "KCNQ2" nucleic acid or its complement under low stringency conditions,
- (iv) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and/or

(v) "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7" (SEQ ID No:265) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7", the variant being encoded by a nucleic acid that hybridizes to the "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising at least 3 but no more than 4 of the following proteins:

(i) "C21ORF57" (SEQ ID No:262) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "C21ORF57", the variant being encoded by a nucleic acid that hybridizes to the "C21ORF57" nucleic acid or its complement under low stringency conditions,

(ii) "Calsenilin" (SEQ ID No:263) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsenilin", the variant being encoded by a nucleic acid that hybridizes to the "Calsenilin" nucleic acid or its complement under low stringency conditions,

(iii) "KCNQ2" (SEQ ID No:264) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KCNQ2", the variant being encoded by a nucleic acid that hybridizes to the "KCNQ2" nucleic acid or its complement under low stringency conditions,

(iv) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,

(v) "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7" (SEQ ID No:265) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7", the variant being encoded by a nucleic acid that hybridizes to the "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the

functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the regulation of transcription.

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:  
expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Calsenilin complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the Calsenilin complex selected from

(i) "C21ORF57" (SEQ ID No:262) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "C21ORF57", the variant being encoded by a nucleic acid that hybridizes to the "C21ORF57" nucleic acid or its complement under low stringency conditions, wherein said low stringency

conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising:

- (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
- (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b) or
- (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and

an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container:

- (a) the complex of any of No. 1 – 8 and/or the proteins of No. 13 and/or
- (b) an antibody according to No. 17 and/or
- (c) a nucleic acid encoding a protein of the complex of any of No. 1 – 8 and/or a protein of No. 13 and/or
- (d) cells expressing the complex of any of No. 1 – 8 and/or a protein of No. 13 and, optionally,
- (e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

21. Array, preferably a microarray, in which at least a complex according to any of No. 1 – 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for modifying a physiological substrate of the complex comprising the step of bringing into contact a complex of any of No. 1 – 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 – 8 and/or any of the following the proteins:

- (i) "C21ORF57" (SEQ ID No:262) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "C21ORF57", the variant being encoded by a nucleic acid that hybridizes to the "C21ORF57" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to a complex of anyone of No. 1 - 8 and/or any of the following the proteins:

- (i) "C21ORF57" (SEQ ID No:262) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "C21ORF57", the variant being encoded by a nucleic acid that hybridizes to the "C21ORF57" nucleic acid or its complement under low stringency conditions, comprising the steps of:
  - (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and
  - (b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:

- (a) exposing said complex, or a cell or organism containing Calsenilin complex to one or more candidate molecules; and
- (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether (i) "C21ORF57" (SEQ ID No:262) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "C21ORF57", the variant being encoded by a nucleic acid that hybridizes to the "C21ORF57" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Calsenilin" (SEQ ID No:263) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsenilin", the variant being encoded by a nucleic acid that hybridizes to the "Calsenilin" nucleic acid or its complement under low stringency conditions, and/or

(iii) "KCNQ2" (SEQ ID No:264) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KCNQ2", the variant being encoded by a nucleic acid that hybridizes to the "KCNQ2" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and/or

(v) "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7" (SEQ ID No:265) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7", the variant being encoded by a nucleic acid that hybridizes to the "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said

complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether

- (i) "C21ORF57" (SEQ ID No:262) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "C21ORF57", the variant being encoded by a nucleic acid that hybridizes to the "C21ORF57" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "Calsenilin" (SEQ ID No:263) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsenilin", the variant being encoded by a nucleic acid that hybridizes to the "Calsenilin" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "KCNQ2" (SEQ ID No:264) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KCNQ2", the variant being encoded by a nucleic acid that hybridizes to the "KCNQ2" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7" (SEQ ID No:265) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7", the variant being encoded by a nucleic acid that hybridizes to the "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as a

neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the regulation of transcription of, or protein composition of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins:

- (i) "C21ORF57" (SEQ ID No:262) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "C21ORF57", the variant being encoded by a nucleic acid that hybridizes to the "C21ORF57" nucleic acid or its complement under low stringency conditions,
- (ii) "Calsenilin" (SEQ ID No:263) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Calsenilin", the variant being encoded by a nucleic acid that hybridizes to the "Calsenilin" nucleic acid or its complement under low stringency conditions,
- (iii) "KCNQ2" (SEQ ID No:264) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "KCNQ2", the variant being encoded by a nucleic acid that hybridizes to the "KCNQ2" nucleic acid or its complement under low stringency conditions,
- (iv) "Presenilin 1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "Presenilin 1", the variant being encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and/or(v) "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7" (SEQ ID No:265) or a

functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7", the variant being encoded by a nucleic acid that hybridizes to the "UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

## 5. PROTOCOLS:

The TAP-technology, which is more fully described in EP 1 105 508 B1 and in Rigaut, et al., 1999, Nature Biotechnol. 17:1030-1032 respectively was used and further adapted as described below for protein purification. Proteins were identified using mass spectrometry as described further below.

### 5.1 Construction of TAP-tagged bait

The cDNAs encoding the complete ORF were obtained by RT-PCR. Total RNA was prepared from appropriate cell lines using the RNeasy Mini Kit (Qiagen). Both cDNA synthesis and PCR were performed with the SUPERScript One-Step RT-PCR for Long templates Kit (Life Technologies) using gene-specific primers. After 35-40 cycles of amplification PCR-products with the expected size were gel-purified with the MinElute PCR Purification Kit (Qiagen) and, if necessary, used for further amplification. Low-abundant RNAs were amplified by nested PCR before gel-purification. Restriction sites for NotI were attached to PCR primers to allow subcloning of amplified cDNAs into the retroviral vectors pIE94-N/C-TAP thereby generating N- or C-terminal fusions with the TAP-tag (Rigaut et al., 1999, Nature Biotechnol. 17:1030-1032). N-terminal tagging was chosen for the following baits/entry points: Presenilin 1, Presenilin 2, Aph-1a, Aph-1b, Pen-2, APP, Tau, Fe65, Calsenilin. C-terminal tagging was chosen for the following baits/entry points: Nicastrin, Aph-1a, Aph-1b, BACE1 D215N, APP, APP695SW, APP-C99, Fe65, X11beta.

Clones were analyzed by restriction digest, DNA sequencing and by in vitro translation using the TNT T7 Quick Coupled Transcription/Translation System (Promega inc.). The presence of the proteins was proven by Western blotting using the protein A part of the TAP-tag for detection. Briefly, separation of proteins by standard SDS-PAGE was followed by semi-dry transfer onto a nitrocellulose membrane (PROTRAN, Schleicher&Schuell) using the MultiphorII blotting apparatus from Pharmacia Biotech. The transfer buffer consisted of 48 mM Tris, 39 mM glycine, 10% methanol and 0,0375% sodium dodecylsulfate. After blocking in phosphate-buffered saline (PBS) supplemented with 10% dry milk powder and 0,1% Tween 20 transferred proteins were probed with the Peroxidase-Anti-Peroxidase Soluble Complex (Sigma) diluted in blocking solution. After intensive washing immunoreactive proteins were visualized by enhanced chemiluminescence (ECL; Amersham Pharmacia Biotech).

## 5.2 Preparation of Virus and infection

As a vector, a MoMLV-based recombinant virus was used.

The preparation has been carried out as follows:

### 5.2.1 Preparation of Virus

293 gp cells were grown to 100% confluency. They were split 1:5 on poly-L-Lysine plates (1:5 diluted poly-L-Lysine [0.01% stock solution, Sigma P-4832] in PBS, left on plates for at least 10 min.). On Day 2, 63 microgram of retroviral Vector DNA together with 13 microgram of DNA of plasmid encoding an appropriate envelope protein were transfected into 293 gp cells (Somia, et al., 1999, Proc. Natl. Acad. Sci. USA 96:12667-12672; Somia, et al. 2000, J. Virol. 74:4420-4424). On Day 3, the medium was replaced with 15 ml DMEM + 10% FBS per 15-cm dish. On Day 4, the medium containing viruses (supernatant) was harvested (at 24 h following medium change after transfection). When a second collection was planned, DMEM 10 % FBS was added to the plates and the plates were incubated for another 24 h. All collections were done as follows: The supernatant was filtered through 0.45 micrometer filter (Corning GmbH, cellulose acetate, 431155). The filter was placed into konical polyallomer centrifuge tubes

(Beckman, 358126) that are placed in buckets of a SW 28 rotor (Beckman). The filtered supernatant was ultracentrifuged at 19400 rpm in the SW 28 rotor, for 2 hours at 21 degree Celsius. The supernatant was discarded. The pellet containing viruses was resuspended in a small volume (for example 300 microliter) of Hank's Balanced Salt Solution [Gibco BRL, 14025-092], by pipetting up and down 100-times, using an aerosol-safe tip. The viruses were used for transfection as described below.

### 5.2.2 Infection

Cells that were infected were plated one day before into one well of a 6-well plate. 4 hours before infection, the old medium on the cells was replaced with fresh medium. Only a minimal volume was added, so that the cells are completely covered (e.g. 700 microliter). During infection, the cells were actively dividing.

A description of the cells and their growth conditions is given in 5.2.3

To the concentrated virus, polybrene (Hexadimethrine Bromide; Sigma, H 9268) was added to achieve a final concentration of 8 microgram/ml (this is equivalent to 2.4 microliter of the 1 milligram/ml polybrene stock per 300 microliter of concentrated retrovirus). The virus was incubated in polybrene at room temperature for 1 hour. For infection, the virus/polybrene mixture was added to the cells and incubated at 37 degree Celsius at the appropriate CO<sub>2</sub> concentration for several hours (e.g. over-day or over-night). Following infection, the medium on the infected cells was replaced with fresh medium. The cells were passaged as usual after they became confluent. The cells contain the retrovirus integrated into their chromosomes and stably express the gene of interest.

### 5.2.3 Cell lines

For expression, SKN-BE2 cells were used. SKN-BE2 cells (American Type Culture Collection-No. CRL-2271) were grown in 95% OptiMEM + 5% iron-supplemented calf serum.

The expression pattern of the TAP-tagged proteins was checked by immunoblot-analysis as described in 5.3.3 and/or by immunofluorescence as described in 5.3.1 or 5.3.2.

### 5.3 Checking of expression pattern of TAP-tagged proteins

The expression pattern of the TAP-tagged protein was checked by immunoblot analysis and/or by immunofluorescence. Immunofluorescence analysis was either carried out according to section 5.3.1 or to section 5.3.2 depending on the type of the TAP-tagged protein. Immunoblot analysis was carried out according to section 5.3.3.

#### 5.3.1 Protocol for the indirect Immunofluorescence staining of fixed mammalian cells for plasma membrane and ER bound proteins

Cells were grown in FCS media on polylysine coated 8 well chamber slides to 50% confluency. Then fixation of the cells was performed in 4% ParaFormaldehyde diluted in Phosphate Buffer Saline (PBS) solution (0.14M Phosphate, 0.1M NaCl pH 7.4). The cells were incubated for 30 minutes at room temperature in 300 microliters per well. Quenching was performed in 0.1M Glycine in PBS for 2x 20 minutes at room temperature. Blocking was performed with 1% Bovine Serum Albumin (BSA) in 0.3% Saponin + PBS for at least 1 hour at room temperature. Incubation of the primary antibodies was performed in the blocking solution overnight at +4°C. The proper dilution of the antibodies was determined in a case to case basis. Cells were washed in PBS containing 0.3% Saponin for 2x 20 minutes at room temperature. Incubation of the secondary antibodies is performed in the blocking solution. Alexa 594 coupled goat anti-rabbit is diluted 1:1000 (Molecular Probes). Alexa 488 coupled goat anti-mouse is diluted 1:1000 (Molecular Probes). DAPI was used to label DNA. If Phalloidin was used to label F-actin, the drug is diluted 1:500 and incubated with the secondary antibodies. Cells were then washed again 2x 20 minutes at room temperature in PBS. The excess of buffer was removed and cells were mounted in a media containing an anti-bleaching agent (Vectashield, Vector Laboratories).

### 5.3.2 Protocol for the indirect Immunofluorescence staining of fixed mammalian cells for non-plasma membrane bound proteins:

Cells were grown in FCS media on Polylysine coated 8 well chamber slides to 50% confluency. Fixation of the cells was performed in 4% ParaFormAldehyde diluted in Phosphate Buffer Saline (PBS) solution (0.14M Phosphate, 0.1M NaCl pH 7.4) for 30 minutes at Room Temperature (RT), 300 microliters per well. Quenching was performed in 0.1M Glycine in PBS for 2x 20 minutes at room temperature. Permeabilization of cells was done with 0.5% Triton X-100 in PBS for 10 minutes at room temperature. Blocking was then done in 1% Bovine Serum Albumin (BSA) in 0.3% Saponin + PBS for at least 1 hour at RT (Blocking solution). Incubation of the primary antibodies was performed in the blocking solution, overnight at +4°C. The proper dilution of the antibodies has to be determined in a case to case basis. Cells were washed in PBS containing 0.3% Saponin, for 2x 20 minutes at RT. Incubation of the secondary antibodies was performed in the blocking solution. Alexa 594 coupled goat anti-rabbit is diluted 1:1000 (Molecular Probes), Alexa 488 coupled goat anti-mouse is diluted 1:1000 (Molecular Probes). DAPI was used to label DNA. If Phalloidin is used to label F-actin, the drug is diluted 1:500 and incubated with the secondary antibodies. Cells were washed 2x 20 minutes at RT in PBS. The excess of buffer was removed and cells were mounted in a media containing an anti-bleaching agent (Vectashield, Vector Laboratories).

### 5.3.3 Immunoblot analysis

To analyze expression levels of TAP-tagged proteins, a cell pellet (from a 6-well dish) was lysed in 60 µl DNase I buffer (5% Glycerol, 100 mM NaCl, 0.8 % NP-40 (IGEPAL), 5 mM magnesium sulfate, 100 µg/ml DNase I (Roche Diagnostics), 50 mM Tris, pH 7.5, protease inhibitor cocktail) for 15 min on ice. Each sample was split into two aliquots. The first half was centrifuged at 13,000 rpm for 5 min. to yield the NP-40-extractable material in the supernatant; the second half (total material) was carefully triturated. 50 µg each of the NP-40-extractable material and the total material are mixed with DTT-containing sample buffer for 30 min at 50°C on a shaker and separated by SDS

polyacrylamide gel electrophoresis on a precast 4-12% Bis-Tris gel (Invitrogen). Proteins were then transferred to nitrocellulose using a semi-dry procedure with a discontinuous buffer system. Briefly, gel and nitrocellulose membrane were stacked between filter papers soaked in either anode buffer (three layers buffer A1 (0.3 M Tris-HCl) and three layers buffer A2 (0.03 M Tris-HCl)) or cathode buffer (three layers of 0.03 M Tris-HCl, pH 9.4, 0.1 % SDS, 40 mM  $\epsilon$ -aminocaproic acid). Electrotransfer of two gels at once was performed at 600 mA for 25 min. Transferred proteins were visualized with Ponceau S solution for one min to control transfer efficiency and then destained in water. The membrane was blocked in 5% non-fat milk powder in TBST (TBS containing 0.05% Tween-20) for 30 min at room temperature. It was subsequently incubated with HRP-coupled PAP antibody (1:5000 diluted in 5% milk/TBST) for 1 h at room temperature, washed three times for 10 min in TBST. The blot membrane was finally soaked in chemiluminescent substrate (ECL, Roche Diagnostics) for 2 min. and either exposed to X-ray film or analyzed on an imaging station.

#### 5.4 Purification of protein complexes

Protein complex purification was adapted to the sub-cellular localization of the TAP-tagged protein and was performed as described below.

##### 5.4.1 Lysate preparation for cytoplasmic proteins

About  $1 \times 10^9$  adherent cells (average) were harvested with a cell scraper and washed 3 times in ice-cold PBS (3 min, 550g). Collected cells were frozen in liquid nitrogen or immediately processed further. For cell lysis, the cell pellet was resuspended in 10 ml of CZ lysis buffer (50 mM Tris-Cl, pH 7.4; 5 % Glycerol; 0,2 % IGEPAL; 1.5 mM  $MgCl_2$ ; 100 mM NaCl; 25 mM NaF; 1 mM  $Na_3VO_4$ ; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and homogenized by 10 strokes of a tight-fitted pestle in a dounce homogenizer. The lysate was incubated for 30 min on ice and spun for 10 min at 20,000g. The supernatant was subjected to an additional ultracentrifugation step for 1 h at 100,000g. The supernatant was recovered and rapidly frozen in liquid nitrogen or immediately processed further.

#### 5.4.2 Lysate preparation for membrane proteins

About  $1 \times 10^9$  adherent cells (average) were harvested with a cell scraper and washed 3 times in ice-cold PBS (3 min, 550g). Collected cells were frozen in liquid nitrogen or immediately processed further. For cell lysis, the cell pellet was resuspended in 10 ml of Membrane-Lysis buffer (50 mM Tris, pH 7.4; 7.5 % Glycerol; 1 mM EDTA; 150 mM NaCl; 25 mM NaF; 1 mM  $\text{Na}_3\text{VO}_4$ ; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and homogenized by 10 strokes of a tight-fitted pestle in a dounce homogenizer. The lysate was spun for 10 min at 750g, the supernatant was recovered and subjected to an ultracentrifugation step for 1 h at 100,000g. The membrane pellet was resuspended in 7.5 ml of Membrane-Lysis buffer containing 0.8% n-Dodecyl- $\beta$ -D-maltoside and incubated for 1 h at 4°C with constant agitation. The sample was subjected to another ultracentrifugation step for 1h at 100,000g and the solubilized material was quickly frozen in liquid nitrogen or immediately processed further.

#### 5.4.3 Lysate preparation for nuclear proteins

About  $1 \times 10^9$  adherent cells (average) were harvested with a cell scraper and washed 3 times in ice-cold PBS (3 min, 550g). Collected cells were frozen in liquid nitrogen or immediately processed further. For cell lysis, the cell pellet was resuspended in 10 ml of Hypotonic-Lysis buffer (10 mM Tris, pH 7.4; 1.5 mM  $\text{MgCl}_2$ ; 10 mM KCl; 25 mM NaF; 1 mM  $\text{Na}_3\text{VO}_4$ ; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and homogenized by 10 strokes of a tight-fitted pestle in a dounce homogenizer. The lysate was spun for 10 min at 2,000g and the resulting supernatant (S1) saved on ice. The nuclear pellet (P1) was resuspended in 5 ml Nuclear-Lysis buffer (50 mM Tris, pH 7.4; 1.5 mM  $\text{MgCl}_2$ ; 20 % Glycerol; 420 mM NaCl; 25 mM NaF; 1 mM  $\text{Na}_3\text{VO}_4$ ; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and incubated for 30 min on ice. The sample was combined with S1, further diluted with 7 ml of Dilution buffer (110 mM Tris, pH 7.4; 0.7 % NP40; 1.5 mM  $\text{MgCl}_2$ ; 25 mM NaF; 1 mM

Na<sub>3</sub>VO<sub>4</sub>; 1 mM DTT), incubated on ice for 10 min and centrifuged at 100,000g for 1h. The final supernatant (S2) was frozen quickly in liquid nitrogen.

#### 5.4.4 Tandem Affinity Purification

The frozen lysate was quickly thawed in a 37°C water bath, and spun for 20 min at 100,000g. The supernatant was recovered and incubated with 0.2 ml of settled rabbit IgG-Agarose beads (Sigma) for 2 h with constant agitation at 4°C. Immobilized protein complexes were washed with 10 ml of CZ lysis buffer (containing 1 Complete™ tablet (Roche) per 50 ml of buffer) and further washed with 5 ml of TEV cleavage buffer (10 mM Tris, pH 7.4; 100 mM NaCl; 0.1 % IGEPAL; 0.5 mM EDTA; 1 mM DTT). Protein-complexes were eluted by incubation with 5 µl of TEV protease (GibcoBRL, Cat.No. 10127-017) for 1 h at 16°C in 150 µl TEV cleavage buffer. The eluate was recovered and combined with 0.2 ml settled Calmodulin affinity beads (Stratagene) in 0.2 ml CBP binding buffer (10 mM Tris, pH 7.4; 100 mM NaCl; 0.1 % IGEPAL; 2mM MgAc; 2mM Imidazole; 1mM DTT; 4 mM CaCl<sub>2</sub>) followed by 1 h incubation at 4°C with constant agitation. Immobilized protein complexes were washed with 10 ml of CBP wash buffer (10 mM Tris, pH 7.4; 100 mM NaCl; 0.1 % IGEPAL; 1mM MgAc; 1mM Imidazole; 1mM DTT; 2 mM CaCl<sub>2</sub>) and eluted by addition of 600 µl CBP elution buffer (10 mM Tris, pH 8.0; 5 mM EGTA) for 5 min at 37°C. The eluate was recovered in a siliconized tube and lyophilized. The remaining Calmodulin resin was boiled for 5 min in 50 µl 4x Laemmli sample buffer. The sample buffer was isolated, combined with the lyophilised fraction and loaded on a NuPAGE gradient gel (Invitrogen, 4-12%, 1.5 mm, 10 well).

#### 5.4.5 Isolation of the Sambiasin complex of the invention from mouse tissue

Two mouse forebrains (0.6314 g total wet weight) were lysed in 14 mls of 50 mM HEPES pH 7.4; 150 mM NaCl; 1 mM EDTA; 0.5 mM Sodium Vanadate; 10% Glycerol; 1% n-Dodecyl-β-D-maltoside containing standard proteinase inhibitors. The tissue was homogenised in a Warring blender for 30 seconds on ice. Homogenates were incubated on ice for 1 hour and then centrifuged at 13,000 g for 30 min at 4°C. The resulting pellet was stored at -80°C while the supernatant was centrifuged at 50,000 g for 30 min at 4°C

and the resulting pellet was also stored at -80°C. 6.5 ml of the supernatant from this second centrifugation step was taken and combined with 25 µl of anti presenilin-1 antisera (MAB5232, Chemicon). The antibody/lysate mixture was incubated for 1 hour at 4°C with end-over end mixing. Pre-washed protein G sepharose was added and the mixture was incubated overnight at 4°C with end-over mixing. The protein G was recovered by centrifugation at 200 g for 5 min at 4°C. The protein G beads were then washed 5 times in 1ml lysis buffer (containing 0.1% n-Dodecyl-β-D-maltoside rather than 1%). 100 µl of NuPAGE sample buffer (Invitrogen) was added and the sample incubated at 37°C for 10 min. Samples were separated on 4-12 % NuPAGE bis/tris gels (Invitrogen, 1.5 mm, 10 well). Proteins were visualized by staining with colloidal coomassie (Sigma) and then analysed by LC/MSMS.

### 5.5 Protein identification by mass spectrometry

#### 5.5.1 Protein digestion prior to mass spectrometric analysis

Gel-separated proteins were reduced, alkylated and digested in gel essentially following the procedure described by Shevchenko et al., 1996, Anal. Chem. 68:850-858. Briefly, gel-separated proteins were excised from the gel using a clean scalpel, reduced using 10 mM DTT (in 5mM ammonium bicarbonate, 54°C, 45 min) and subsequently alkylated with 55 mM iodoacetamid (in 5 mM ammonium bicarbonate) at room temperature in the dark (30 min). Reduced and alkylated proteins were digested in gel with porcine trypsin (Promega) at a protease concentration of 12.5 ng/µl in 5mM ammonium bicarbonate. Digestion was allowed to proceed for 4 hours at 37°C and the reaction was subsequently stopped using 5 µl 5% formic acid.

#### 5.5.2 Sample preparation prior to analysis by mass spectrometry

Gel plugs were extracted twice with 20 µl 1% TFA and pooled with acidified digest supernatants. Samples were dried in a vacuum centrifuge and resuspended in 13 µl 1% TFA.

### 5.5.3 Mass spectrometric data acquisition

Peptide samples were injected into a nano LC system (CapLC, Waters or Ultimate, Dionex) which was directly coupled either to a quadrupole TOF (QTOF2, QTOF Ultima, QTOF Micro, Micromass or QSTAR Pulsar, Sciex) or ion trap (LCQ Deca XP) mass spectrometer. Peptides were separated on the LC system using a gradient of aqueous and organic solvents (see below). Solvent A was 5% acetonitrile in 0.5% formic acid and solvent B was 70% acetonitrile in 0.5% formic acid.

Time (min)	% solvent A	% solvent B
0	95	5
5.33	92	8
35	50	50
36	20	80
40	20	80
41	95	5
50	95	5

Peptides eluting off the LC system were partially sequenced within the mass spectrometer.

### 5.5.4 Protein identification

The peptide mass and fragmentation data generated in the LC-MS/MS experiments were used to query fasta formatted protein and nucleotide sequence databases maintained and updated regularly at the NCBI (for the NCBI nr, dbEST and the human and mouse genomes) and European Bioinformatics Institute (EBI, for the human, mouse, *D. melanogaster* and *C. elegans* proteome databases). Proteins were identified by correlating the measured peptide mass and fragmentation data with the same data computed from the entries in the database using the software tool Mascot (Matrix Science; Perkins et al., 1999, *Electrophoresis* 20:3551-3567). Search criteria varied depending on which mass spectrometer was used for the analysis.

TABLE 1

## COMPONENTS OF COMPLEXES

Name of complex	Entry Point	All interactors of the complex	Known interactors of the complex	Novel interactors of the complex	Proteins of unknown function
Presenilin 1 complex	Presenilin 1	Alpha catenin	Alpha catenin	BAX inhibitor 1	CGI-147
		Aph-1a	Aph-1a	Cadherin-11 precursor	FKRP
		BAX inhibitor 1	Beta catenin	Cadherin-4 precursor	FLJ20627
		Beta catenin	Delta-2 catenin	CGI-147	MGC5442
		Cadherin-11 precursor	Gamma catenin	FKRP	Sterile alpha and HEAT/Armadillo motif protein
		Cadherin-4 precursor	Nicastrin	FLJ20627	
		CGI-147	Delta-1 catenin	MGC5442	
		Delta-2 catenin	Pen-2	Sterile alpha and HEAT/Armadillo motif protein	
		FKRP	Plakophilin 4	Sortilin 1	
		FLJ20627	Presenilin 1		
		Gamma catenin	Ubiquitin		

		MGC5442				
		Nicastrin				
		Delta-1 catenin				
		Pen-2				
		Plakophilin 4				
		Presenilin 1				
		Sortilin 1				
		Sterile alpha and HEAT/Armadillo motif protein				
		Ubiquilin				
Presenilin 2 complex	Presenilin 2	18 kDa microsomal signal peptidase subunit	DOCK3	18 kDa microsomal signal peptidase subunit	Cerebral protein-10	
		200 kDa proteasome activator	Nicastrin	200 kDa proteasome activator	CGI-51	
		Acetolactate synthase	Presenilin 2	Acetolactate synthase	DKFZp586c1924	
		ADP-ribosylation factor 3		ADP-ribosylation factor 3	FLJ20342	
		Adrenoleukodystrophy protein		Adrenoleukodystrophy protein	FLJ20420	

	ATP-binding cassette protein, sub-family B, member 1		ATP-binding cassette protein, sub-family B, member 1	FLJ22555
	ATP-dependent metalloprotease FtsH1 homologue		ATP-dependent metalloprotease FtsH1 homologue	FLJ22678
	Calcium-binding protein P22		Calcium-binding protein P22	KIAA0062
	Cation-chloride cotransporter- interacting protein		Cation-chloride cotransporter- interacting protein	KIAA0090
	Centromere/kinetochor e protein ZW10 homologue		Centromere/kinetochore protein ZW10 homologue	KIAA0103
	Cerebral protein-10		Cerebral protein-10	KIAA1499
	CGI-51		CGI-51	MGC4248
	DKFZp586c1924		DKFZp586c1924	NICE-3
	DOCK3		Down syndrome critical region protein 2	
	Down syndrome critical region protein 2		ECSIT	
	ECSIT		FLJ20342	

	FLJ20342		FLJ20420	
	FLJ20420		FLJ22555	
	FLJ22555		FLJ22678	
	FLJ22678		Galactosylgalactosylxy losylprotein 3-beta- glucuronosyltransferas e 3	
	Galactosylgalactosylxy losylprotein 3-beta- glucuronosyltransferas e 3		HTRA2	
	HTRA2		HU-K4	
	HU-K4		KIAA0062	
	KIAA0062		KIAA0090	
	KIAA0090		KIAA0103	
	KIAA0103		KIAA1499	
	KIAA1499		MGC4248	
	MGC4248		NICE-3	
	Nicestrin		NPD002	
	NICE-3		P63 protein	
	NPD002		Prohibitin	

	P63 protein		Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3	
	Presenilin 2		PSMA1	
	Prohibitin		PSMA3	
	Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3		PSMA4	
	PSMA1		PSMA6	
	PSMA3		PSMB1	
	PSMA4		PSMB2	
	PSMA6		PSMB3	
	PSMB1		PSMB4	
	PSMB2		PSMB5	
	PSMB3		PSMB6	
	PSMB4		PSMC1	
	PSMB5		PSMC2	
	PSMB6		PSMC3	
	PSMC1		PSMC4	
	PSMC2		PSMC5	

	PSMC3		PSMC6	
	PSMC4		PSMD1	
	PSMC5		PSMD11	
	PSMC6		PSMD12	
	PSMD1		PSMD13	
	PSMD11		PSMD2	
	PSMD12		PSMD3	
	PSMD13		PSMD4	
	PSMD2		Serine/threonine protein phosphatase 6	
	PSMD3		Sortilin 1	
	PSMD4		Stearoyl-CoA desaturase	
	Serine/threonine protein phosphatase 6		Ubiquitin-protein ligase EDD	
	Sortilin 1		Voltage-dependent anion channel 2	
	Stearoyl-CoA desaturase		Wolframin	
	Ubiquitin-protein ligase EDD			

		Voltage-dependent anion channel 2				
		Wolfamin				
Nicastrin complex	Nicastrin	18 kDa microsomal signal peptidase subunit	Aph-1a	18 kDa microsomal signal peptidase subunit	ATP-binding cassette, sub-family A, member 3	
		25 kDa microsomal signal peptidase subunit	BACE1	25 kDa microsomal signal peptidase subunit	CGI-13	
		Aph-1a	Nicastrin	ATP-binding cassette, sub-family A, member 3	ENSG00000144840	
		ATP-binding cassette, sub-family A member 3	Pen-2	BSCv protein	FLJ20342	
		BACE1	Presenilin-1	Casein kinase II beta chain	FLJ20481	
		BSCv protein	Presenilin-2	Cathepsin B	FLJ22390	
		Casein kinase II beta chain		CGI-13	Hypothetical protein tyrosine phosphatase	ensg00000149185

	Cathepsin B		Delta-6 fatty acid desaturase	KIAA1181
	CGI-13		ENSG00000144840	KIAA1533
	Delta-6 fatty acid desaturase		FLJ13977	PP1, regulatory subunit 15B
	ENSG00000144840		FLJ20342	RING finger protein 5
	FLJ13977		FLJ20481	Thioredoxin domain-containing protein
	FLJ20342		FLJ22390	
	FLJ20481		Hypothetical protein tyrosine phosphatase ensg00000149185	
	FLJ22390		ICAM-2	
	Hypothetical protein tyrosine phosphatase ensg00000149185		KIAA1181	
	ICAM-2		KIAA1533	
	KIAA1181		Mesenchymal stem cell protein DSCD75	
	KIAA1533		Neurotrypsin	

	Mesenchymal stem cell protein DSCD75		NICE-3	
	Neurotrypsin		Protein amplified in osteosarcoma (OS-9)	
	Nicastrin		PP1, regulatory subunit 15B	
	NICE-3		Protein similar to stromal cell-derived factor 2	
	Pen-2		Protocadherin beta 8	
	Presenilin-1		REP8 protein	
	Presenilin-2		Retinal short-chain dehydrogenase/reductase retSDR2	
	Protein amplified in osteosarcoma (OS-9)		RING finger protein 5	
	PP1, regulatory subunit 15B		Stromal cell-derived factor 2-like 1	
	Protein similar to stromal cell-derived factor 2		Thioredoxin domain-containing protein	

		Protocadherin beta 8		Voltage-dependent anion channel 1	
		REP8 protein			
		Retinal short-chain dehydrogenase/reductase retSDR2			
		RING finger protein 5			
		Stromal cell-derived factor 2-like 1			
		Thioredoxin domain-containing protein			
		Voltage-dependent anion channel 1			
Aph-1a complex	Aph-1a	18 kDa microsomal signal peptidase subunit	Aph-1a	18 kDa microsomal signal peptidase subunit	Cerebral protein-10
		25 kDa microsomal signal peptidase subunit	APP	25 kDa microsomal signal peptidase subunit	CGI-13
		Aph-1a	Nicastrin	Brain-specific GTP-binding protein	KIAA0062
		APP	Pen-2	Cerebral protein-10	KIAA0251

	Brain-specific GTP-binding protein	Presenilin 1	CGI-13	KIAA0363
	Cerebral protein-10	Presenilin 2	Dihydrofolate reductase	KIAA0971
	CGI-13		Endocytic receptor Endo180	KIAA1250
	Dihydrofolate reductase		FLJ13660	Mesenchymal stem cell protein DSCD75
	Endocytic receptor Endo180		HU-K4	Protocadherin 7
	FLJ13660		Integral membrane protein 2B (ITM2B)	Protocadherin beta 16
	HU-K4		KIAA0062	Protocadherin beta 8
	Integral membrane protein 2B (ITM2B)		KIAA0251	Retinal short-chain dehydrogenase/reductase retSDR2
	KIAA0062		KIAA0363	Sterile alpha and heat/armadillo motif protein

	KIAA0251		KIAA0971	Thioredoxin domain-containing protein
	KIAA0363		KIAA1250	Vacuolar ATP synthase membrane sector associated protein m8-9
	KIAA0971		Mesenchymal stem cell protein DSCD75	
	KIAA1250		Neurotrypsin	
	Mesenchymal stem cell protein DSCD75		PP2C gamma	
	Neurotrypsin		Protocadherin 7	
	Nicastrin		Protocadherin beta 16	
	Pen-2		Protocadherin beta 8	
	PP2C gamma		RAB-18	
	Presenilin 1		Rab3 GTPase-activating protein, non-catalytic subunit	

	Presentilin 2		Retinal short-chain dehydrogenase/reductase retSDR2	
	Protocadherin 7		Sideroflexin 1	
	Protocadherin beta 16		Signal transducer and activator of transcription-1	
	Protocadherin beta 8		SMAP-1B	
	RAB-18		Sterile alpha and heat/armadillo motif protein	
	Rab3 GTPase-activating protein, non-catalytic subunit		Sterol O-acyltransferase 1	
	Retinal short-chain dehydrogenase/reductase retSDR2		Thioredoxin domain-containing protein	
	Sideroflexin 1		Triple functional domain protein (PTPRF interacting)	

		Signal transducer and activator of transcription-1		Vacuolar ATP synthase membrane sector associated protein m8-9	
		SMAP-1B			
		Sterile alpha and heat/armadillo motif protein			
		Sterol O-acyltransferase 1			
		Thioredoxin domain-containing protein			
		Triple functional domain protein (PTPRF interacting)			
		Vacuolar ATP synthase membrane sector associated protein m8-9			
Aph-1b complex	Aph-1b	18 kDa microsomal signal peptidase subunit	Aph-1b	18 kDa microsomal signal peptidase subunit	Autocrine motility factor receptor

	23 kDa microsomal signal peptidase subunit	Nicastrin	23 kDa microsomal signal peptidase subunit	FLJ10737
	25 kDa microsomal signal peptidase subunit	Pen-2	25 kDa microsomal signal peptidase subunit	FLJ14560
	Activating transcription factor 6	Presenilin 1	Activating transcription factor 6	KIAA0363
	Aph-1a	Presenilin 2	Aph-1a	Protocadherin beta 8a
	Aph-1b		APP	Protocadherin gamma C3
	APP		Autocrine motility factor receptor	
	Autocrine motility factor receptor		Calsyntenin 1	
	Calsyntenin 1		cAMP responsive element binding protein-like 1	
	cAMP responsive element binding protein-like 1		Delta-1 catenin	

	Delta-1 catenin		FLJ10737	
	FLJ10737		FLJ14560	
	FLJ14560		HU-K4	
	HU-K4		KIAA0363	
	KIAA0363		PAS domain containing serine/threonine kinase	
	Nicastrin		Polycystin 2	
	PAS domain containing serine/threonine kinase		PP2C gamma	
	Pen-2		Protocadherin beta 8a	
	Polycystin 2		Protocadherin gamma C3	
	PP2C gamma		Voltage-dependent anion channel 3	
	Presenilin 1			
	Presenilin 2			
	Protocadherin beta 8a			
	Protocadherin gamma C3			

		Voltage-dependent anion channel 3				
Pen-2 complex	Pen-2	Alpha-2 catenin	Aph-1a	Alpha-2 catenin	KIAA1102	
		Aph-1a	Nicastrin	Copine III	MGC2803	
		Copine III	Pen-2	Dachshund 2	TNRC15	
		Dachshund 2	Presenilin 1	Delta-1 catenin		
		Delta-1 catenin		KIAA1102		
		KIAA1102		MGC2803		
		MGC2803		Presenilin 2		
		Nicastrin		TNRC15		
		Pen-2		TPST1		
		Presenilin 1		ZIP kinase		
		Presenilin 2				
		TNRC15				
		TPST1				
		ZIP kinase				
BACE1 D215N complex	BACE1 D215N	Acetylcholine receptor beta-4	BACE1 D215N	Acetylcholine receptor beta-4	MGC4248	
		ADP-ribosylation factor 4	Nicastrin	ADP-ribosylation factor 4	Protocadherin beta 7	

	APP		APP	
	BACE1 D215N		Calcium binding protein Cab45	
	Calcium binding protein Cab45		Delta-like homologue	
	Delta-like homologue		DNAJC3	
	DNAJC3		Fe65	
	Fe65		KIAA0747	
	KIAA0747		MGC4248	
	MGC4248		Neural cell adhesion molecule L1	
	Neural cell adhesion molecule L1		Neurotrypsin	
	Neurotrypsin		Protein amplified in osteosarcoma (OS-9)	
	Nicastrin		Protocadherin beta 10	
	Protein amplified in osteosarcoma (OS-9)		Protocadherin beta 14	
	Protocadherin beta 10		Protocadherin beta 7	
	Protocadherin beta 14		Protocadherin gamma C3	
	Protocadherin beta 7		S-100 alpha	

		Protocadherin gamma		Seipin	
		C3		SEL-1 homologue	
		S-100 alpha		Stromal cell-derived factor 2-like 1	
		Seipin			
		SEL-1 homologue			
		Stromal cell-derived factor 2-like 1			
APP complex	APP	APP	APP	Bcl-XL-binding protein v68	FLJ10773
		Bcl-XL-binding protein v68	Fe65	FLJ10773	
		Fe65	Fe65L1	Neurotrypsin	
		Fe65L1	JIP-1	S-100 alpha	
		FLJ10773	X11beta	S-100 beta	
		JIP-1			
		Neurotrypsin			
		S-100 alpha			
		S-100 beta			
		X11beta			
APP695SW complex	APP695SW	APP695SW	APP695SW	FLJ10773	FLJ10773

	Fe65	Fe65	Integral membrane protein 2B (ITM2B)	
	Fe65L1	Fe65L1	S-100 alpha	
	FLJ10773	JIP-1		
	Integral membrane protein 2B (ITM2B)	X11beta		
	JIP-1			
	S-100 alpha			
	X11beta			
APP-C99 complex	APP	APP-C99		KIAA1102
	APP-C99	Fe65		KIAA1949
	Delta-like homologue	Fe65L1		MGC4022
	Fe65	X11beta		MGC5442
	Fe65L1			
	Integral membrane transporter protein			
	KIAA1102			
	KIAA1949			
	MGC4022			
	MGC5442			
	NAP-1 related protein			

		Neurocalcin delta			
		REST corepressor			
		S-100 alpha			
		S-100 beta			
		X11beta			
Tau complex	Tau	14-3-3 protein zeta/delta	14-3-3 protein zeta/delta	Deoxyhypusine synthase	MEP50
		Actin	Actin	Dynactin 2	
		Alpha tubulin	Alpha tubulin	MEP50	
		Beta tubulin	Beta tubulin	Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1	
		Deoxyhypusine synthase	PPP2CA (PP2A, catalytic subunit, alpha)	PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)	
		Dynactin 2	PPP2CB (PP2A, catalytic subunit, beta)	S100 beta	
		MEP50	PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)		

		Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1	PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)		
		PPP2CA (PP2A, catalytic subunit, alpha)	Tau		
		PPP2CB (PP2A, catalytic subunit, beta)			
		PPP2R1A (PP2A, 65 KDA regulatory subunit A, alpha)			
		PPP2RBA, (PP2A, 55 KDA regulatory subunit B, alpha)			
		S100 beta			
		Tau			
X11beta complex	X11beta	ADAMTS-19	APP	APLP1	ADAMTS-19
		APLP1	Munc18-1	ADAMTS-19	Cadherin EGF LAG seven-pass G-type receptor 2

	APP	Neurexin-1	Axonemal dynein heavy chain 8	Calsyntenin-2
	Axonemal dynein heavy chain 8	Syntaxin-1	Cadherin EGF LAG seven-pass G-type receptor 2	Calsyntenin-3
	Cadherin EGF LAG seven-pass G-type receptor 2	X11beta	Calsyntenin-1	ENG00000168820 (hypothetical protein with p-loop)
	Calsyntenin-1		Calsyntenin-2	FLJ13910
	Calsyntenin-2		Calsyntenin-3	HERC2 protein
	Calsyntenin-3		Chondroitin sulfate proteoglycan 6	HSPC154
	Chondroitin sulfate proteoglycan 6		Chromatin-specific transcription elongation factor FACT 140 kDa subunit	HSPC245
	Chromatin-specific transcription elongation factor FACT 140 kDa subunit		DC6 protein	KIAA0056
	DC6 protein		Dynein light chain-A	KIAA0166
	Dynein light chain 2A		Dynein light chain 2A	KIAA0564

	Dynein light chain-A		ENG00000168820 (hypothetical protein with p-loop)	KIAA0763	•
	ENG00000168820 (hypothetical protein with p-loop)		Eukaryotic translation initiation factor 4A, isoform	MEGF7	
	Eukaryotic translation initiation factor 4A, isoform		FLJ13910	NIPSNAP1	
	FLJ13910		FRAP1	Paladin	
	FRAP1		GTP-binding protein ERA	PDZ and LIM domain protein 1	
	GTP-binding protein ERA		HDAC2	PILT	
	HDAC2		HERC2 protein	Programmed cell death 10	
	HERC2 protein		HSPC154	Protein similar to AGCP6688	
	HSPC154		HSPC245	Ubiquitin-protein ligase E3-alpha	
	HSPC245		IKAP		

	IKAP		Insulinoma- glucagonoma protein 20	
	Insulinoma- glucagonoma protein 20		KIAA0056	
	KIAA0056		KIAA0166	
	KIAA0166		KIAA0325	
	KIAA0325		KIAA0564	
	KIAA0564		KIAA0763	
	KIAA0763		Laminin, gamma 1	
	Laminin, gamma 1		LIB ( leucine-rich repeat protein)	
	LIB ( leucine-rich repeat protein)		MBIP	
	MBIP		MEGF7	
	MEGF7		Myosin IXB	
	Munc18-1		NIPSNAP1	
	Myosin IXB		NIPSNAP2	
	Neurexin-1		Paladin	
	NIPSNAP1		PDZ and LIM domain protein 1	

	NIPSNAP2		Peroxioreoxin 4	
	Paladin		Phosphoenolpyruvate carboxykinase 2 (mitochondrial)	
	PDZ and LIM domain protein 1		PILT	
	Peroxioreoxin 4		Procollagen C-endopeptidase enhancer	
	Phosphoenolpyruvate carboxykinase 2 (mitochondrial)		Programmed cell death 10	
	PILT		Protein similar to AGCP6688	
	Procollagen C-endopeptidase enhancer		Reelin	
	Programmed cell death 10		RPGR-interacting protein 1	
	Protein similar to AGCP6688		Serine/threonine protein phosphatase 6	

	Reelin		Sortilin-related receptor	
	RPGR-interacting protein 1		Synaptogyrin 3	
	Serine/threonine protein phosphatase 6		Ubiquitin-protein ligase E3-alpha	
	Sortilin-related receptor		VEGF nerve growth factor inducible protein	
	Synaptogyrin 3		Zinc finger protein 198	
	Syntaxin-1			
	Ubiquitin-protein ligase E3-alpha			
	VEGF nerve growth factor inducible protein			
	X11beta			
	Zinc finger protein 198			
Fe65 complex	Fe65	14-3-3 protein epsilon	14-3-3 protein epsilon	Krab box protein ensp000000302970
		14-3-3 protein beta/alpha	14-3-3 protein beta/alpha	Protein similar to probable mitotic centromere associated kinesin

	14-3-3 protein eta	APP	14-3-3 protein eta	Zinc finger protein 277
	14-3-3 protein gamma	APP-C99	14-3-3 protein gamma	
	14-3-3 protein tau	Fe65	14-3-3 protein tau	
	14-3-3 protein zeta/delta	RNB6	14-3-3 protein zeta/delta	
	APLP1	Transcription factor CP2	ATP-binding cassette, sub-family B, member 7	
	APLP2		ECP-51	
	APP		GAP-associated tyrosine phosphoprotein p62	
	APP-C99		Integral membrane protein 2B (ITM2B)	
	ATP-binding cassette, sub-family B, member 7		Krab box protein ensp00000302970	
	ECP-51		PDZ domain protein MAGI-3	

	Fe65		PPP2RBA (55 kDa regulatory subunit B, alpha)	
	GAP-associated tyrosine phosphoprotein p62		Protein similar to probable mitotic centromere associated kinesin	
	Integral membrane protein 2B (ITM2B)		Spliceosome protein SAP-62	
	Krab box protein ensp00000302970		Zinc finger protein 277	
	PDZ domain protein MAGI-3			
	PPP2RBA (55 kDa regulatory subunit B, alpha)			
	Protein similar to probable mitotic centromere associated kinesin			
	RNB6			

		Spliceosome protein SAP-62				
		Transcription factor CP2				
		Zinc finger protein 277				
Calsenilin complex	Calsenilin	C21ORF57	Calsenilin	C21ORF57	C21ORF57	
		Calsenilin	Presenilin 1	KCNQ2		
		KCNQ2		UDP- GalNAc:polypeptide N- acetylglactosaminyltr ansferase 7		
		Presenilin 1				
		UDP- GalNAc:polypeptide N- acetylglactosaminyltra nsferase 7				

TABLE 2

## INDIVIDUAL PROTEINS OF THE COMPLEXES

Protein name	SEQ ID	IPI number	Molecular weight
14-3-3 protein epsilon	21	IP100000816.1	29174
14-3-3 protein beta/alpha	22	IP100013889.1	27951
14-3-3 protein eta	23	IP100030286.1	28088
14-3-3 protein eta	24	IP100033598.1	28171
14-3-3 protein gamma	25	IP100018146.1	27764
14-3-3 protein tau	26	IP100021263.1	27745
14-3-3 protein zeta/delta	98	IP100104128.1	20625
18 kDa microsomal signal peptidase subunit	99	IP100005260.1	206407
200 kDa proteasome activator	206	IP100030262.2	20253
23 kDa microsomal signal peptidase subunit	159	IP100014148.1	25003
25 kDa microsomal signal peptidase subunit	103	IP100009963.2	67868
Acetolactate synthase	252	IP100097981.1	63202
Acetylcholine receptor beta-4	240	IP100021439.1	41737
Actin	207	IP100002511.1	74567
Activating transcription factor 6	44	IP100152639.1	134062
ADAMTS-19	100	IP100029248.1	20470
ADP-ribosylation factor 3	251	IP100029743.1	20380
ADP-ribosylation factor 4			

Adrenoleukodystrophy protein	104	IP100017637.1	82909
Alpha catenin	1	IP100017291.1	100071
Alpha tubulin	241	IP100142632.1	50152
Alpha-2 catenin	218	IP100030907.1	105282
Aph-1a	2	IP100059964.1	28996
Aph-1b (Sambiasin-2)	208	IP100103233.1	28460
APLP1	27	IP100020012.1	72202
APLP2	28	IP100031030.1	86956
APP	29	IP100006608.1	86943
APP695SW	232		78630
APP-C99	30		11277
ATP-binding cassette protein, sub-family B, member 1	101	IP100027481.1	141463
ATP-binding cassette, sub-family A, member 3	160	IP100017800.1	191388
ATP-binding cassette, sub-family B, member 7	31	IP100023879.1	82641
ATP-dependent metalloprotease FtsH1 homologue	102	IP100045946.1	86503
Autocrine motility factor receptor	209	IP100038908.1	73022
Axonemal dynein heavy chain 8	45	IP100014845.4	515950
BACE1	161	IP100011518.1	55764
BACE1 D215N	266		55764
BAX inhibitor 1	3	IP100022748.2	26538
Bcl-XL-binding protein v68	226	IP100063242.1	28006

Beta catenin	4	IP100017292.1	85497
Beta tubulin	242	IP100142634.1	49671
Brain-specific GTP-binding protein	187	IP100103530.1	63543
BSCv protein	162	IP100031131.1	46480
C21ORF57	262	IP100067923.1	33515
Cadherin EGF LAG seven-pass G-type receptor 2	46	IP100015346.1	317453
Cadherin-11 precursor	6	IP100024037.1	88049
Cadherin-4 precursor	7	IP100040836.3	74308
Calcium binding protein Cab45	253	IP100106646.1	41807
Calcium-binding protein P22	106	IP100016987.1	22325
Calsenilin	263	IP100032530.1	29231
Calsyntenin 1	47	IP100007257.1	109793
Calsyntenin-2	48	IP100005491.1	107020
Calsyntenin-3	49	IP100156997.1	106098
cAMP responsive element binding protein-like 1	217	IP100004084.3	76709
Casein kinase II beta chain	164	IP100010865.1	24942
Cathepsin B	165	IP100013478.1	37808
Cation-chloride cotransporter-interacting protein	107	IP100024998.1	96171
Centromere/kinetochore protein ZW10 homologue	108	IP100011631.1	88829
Cerebral protein-10	109	IP100018730.1	52118
CGI-13	163	IP100008847.1	52917

CGI-78		268	GenBank AAD34072	27320
CGI-147		5	IP100032903.1	19194
CGI-51		105	IP100000985.1	51962
Chondroitin sulfate proteoglycan 6		50	IP100023102.1	141542
Chromatin-specific transcription elongation factor FACT 140 kDa subunit		51	IP100026970.1	119914
Copine III		219	IP100024403.1	60131
Dachshund 2		220	IP100065787.1	65323
DC6 protein		52	IP100024620.1	11529
Delta-1 catenin		8	IP100015202.1	104958
Delta-2 catenin		9	IP100033469.2	132665
Delta-6 fatty acid desaturase		166	IP100003544.1	52259
Delta-like homologue		233	IP100009191.1	41143
Deoxyhypusine synthase		243	IP100026829.1	40971
Dihydrofolate reductase		188	IP100016816.1	21322
DKFZp586c1924		110	IP100031064.1	21527
DNAJC3		254	IP100006713.1	57580
DOCK3		111	IP100004422.1	218952
Down syndrome critical region protein 2		112	IP100030770.1	32854
Dynactin 2		244	IP100013802.2	44231
Dynein light chain 2A		53	IP100023551.1	10922
Dynein light chain-A		54	IP100007675.1	56627

ECP-51		32	PI00009104.1	51157
ECSIT		113	PI00106506.1	49148
Endocytic receptor Endo180		189	PI00005707.3	166655
ENG00000168820 (hypothetical protein with p-loop)		55	PI00151716.2	30772
ENSG00000144840		167	PI00102897.1	26308
Eukaryotic translation initiation factor 4A, isoform		56	PI00025491.1	46154
Fe65		33	PI00010843.1	77244
Fe65L1		228	PI00023841.1	81080
FKRP		10	PI00013281.1	54568
FLJ10737		210	PI00018910.1	63336
FLJ10773		227	PI00018944.1	20345
FLJ13660		190	PI00100927.1	56921
FLJ13910		57	PI00009707.1	43993
FLJ13977		168	PI00025520.1	53482
FLJ14560		211	PI00013638.1	44876
FLJ20342		114	PI00015713.1	65084
FLJ20420		115	PI00015833.1	26152
FLJ20481		169	PI00016418.1	47655
FLJ20627		11	PI00016673.1	51618
FLJ22390		170	PI00009343.1	17098
FLJ22555		116	PI00103303.1	32545

FLJ22678		117	IP100002193.1	58355
FRAP1		58	IP100031410.1	288892
Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3		118	IP100014931.1	37062
Gamma catenin		12	IP100028128.1	81498
GAP-associated tyrosine phosphoprotein p62		34	IP100008575.1	48227
GTP-binding protein ERA		59	IP100026512.1	49098
HDAC2		60	IP100023289.1	55325
HERC2 protein		61	IP100005826.1	527472
HSPC154		62	IP100107156.1	28202
HSPC245		63	IP100025598.2	14124
HTRA2		119	IP100001663.1	48841
HU-K4		120	IP100163951.1	48771
Hypothetical protein tyrosine phosphatase ensg00000149185		171	IP100102935.1	22844
ICAM-2		172	IP100009477.1	30653
IKAP		64	IP100028877.1	150191
Insulinoma-glucagonoma protein 20		65	IP100103536.1	183267
Integral membrane protein 2B (ITM2B)		35	IP100031821.1	30338
Integral membrane transporter protein		234	IP100020093.1	31735
JIP-1		229	IP100023133.1	77524
KCNQ2		264	IP100012858.1	95848
KIAA0056		66	IP100000899.1	169718

KIAA0062	121	PI00014236.1	58417
KIAA0090	122	PI00160376.1	111759
KIAA0103	123	PI00014149.1	34833
KIAA0166	67	PI00001458.1	250749
KIAA0251	191	PI00010861.1	90027
KIAA0325	68	PI00141330.2	532367
KIAA0363	192	PI00004538.1	156999
KIAA0564	69	PI00158296.1	171891
KIAA0747	255	PI00022143.1	122856
KIAA0763	70	PI00006669.1	94914
KIAA0971	193	PI00007231.1	74536
KIAA1102	221	PI00160387.1	121739
KIAA1181	173	PI00003635.1	36879
KIAA1250	194	PI00033429.1	197211
KIAA1499	124	PI00001676.1	73788
KIAA1533	174	PI00001841.1	72964
KIAA1949	235	PI00150950.1	67959
Krab box protein ensp00000302970	36	PI00154267.1	37912
Laminin, gamma 1	72	PI00003398.1	177607
LIB ( leucine-rich repeat protein)	71	PI00057018.2	64414
MBIP	73	PI00009868.1	39236

MEGF7		74	IP100023954.2	175609
MEP50		245	IP100012202.1	36724
Mesenchymal stem cell protein DSCD75		175	IP100010292.1	23865
MGC2803		222	IP100031526.1	18419
MGC4022		236	IP100010625.1	59797
MGC4248		125	IP100031582.1	24274
MGC5442		13	IP100027773.1	26261
Munc18-1		75	IP100046057.1	68736
Myosin IXB		76	IP100003064.1	228624
NAP-1 related protein		237	IP100155244.1	44159
Neural cell adhesion molecule L1		256	IP100027087.1	140003
Neurexin-1		79	IP100006314.1	161883
Neurocalcin delta		238	IP100149712.1	22114
Neurotrypsin		176	IP100011063.1	97012
Nicestrin		14	IP100021983.1	78411
NICE-3		126	IP100032413.1	28779
NIPSNAP1		77	IP100021086.2	33310
NIPSNAP2		78	IP100016077.1	33743
NPD002		127	IP100152981.1	68760
Nuclear receptor co-repressor/HDAC3 complex subunit TBLR1		246	IP100002922.2	55595
P63 protein		128	IP100141318.1	66022

Paladin	82	IP100161782.1	96754
PAS domain containing serine/threonine kinase	212	IP100141040.1	142859
PDZ and LIM domain protein 1	80	IP100010414.2	36072
PDZ domain protein MAGI-3	37	IP100022491.1	111914
Pen-2	15	IP100020516.1	12029
Peroxiredoxin 4	83	IP100011937.1	30540
Phosphoenolpyruvate carboxykinase 2 (mitochondrial)	84	IP100004383.1	70637
PILT	81	IP100010544.2	60705
Plakophilin 4	16	IP100021076.1	134269
Polycystin 2	213	IP100013807.1	109790
PP1, regulatory subunit 15B	177	IP100045837.1	79125
PP2C gamma	195	IP100006167.1	59272
PPP2CA (PP2A, catalytic subunit, alpha)	247	IP100008380.1	35594
PPP2CB (PP2A, catalytic subunit, beta)	248	IP100003461.1	35575
PPP2R1A (PP2A, 65 kDa regulatory subunit A, alpha)	249	IP100025326.1	65092
PPP2RBA (PP2A, 55 kDa regulatory subunit B, alpha)	38	IP100020852.1	51692
Presenilin 1	17	IP100026333.1	52163
Presenilin 2	152	IP100028485.1	50140
Procollagen C-endopeptidase enhancer	85	IP100014828.1	47972
Programmed cell death 10	86	IP100026997.1	24658
Prohibitin	153	IP100017334.1	29804

Protein amplified in osteosarcoma (OS-9)	178	IP100013268.1	75562
Protein similar to AGCP6688	87	IP100140709.1	14290
Protein similar to cholinergic receptor, nicotinic, alpha polypeptide 3	154	IP100007259.1	55637
Protein similar to probable mitotic centromere associated kinesin	39	IP100088667.1	126801
Protein similar to stromal cell-derived factor 2	179	IP100034198.1	23026
Protocadherin 7	196	IP100001893.2	116105
Protocadherin beta 10	257	IP100009034.1	87621
Protocadherin beta 14	258	IP100001434.1	87548
Protocadherin beta 16	197	IP100016595.1	84936
Protocadherin beta 7	259	IP100001425.1	86707
Protocadherin beta 8	180	IP100009033.1	87624
Protocadherin beta 8a	214	IP100045607.1	84983
Protocadherin gamma C3	215	IP100001872.3	101077
PSMA1	129	IP100016832.1	29556
PSMA3	130	IP100016834.1	28302
PSMA4	131	IP100016836.1	29484
PSMA6	132	IP100029623.1	27399
PSMB1	133	IP100025019.1	26489
PSMB2	134	IP100028006.1	22836
PSMB3	135	IP100028004.2	22949
PSMB4	136	IP100000806.1	29192

PSMB5	137	IP100000814.1	22897
PSMB6	138	IP100000811.2	25358
PSMC1	139	IP100011126.2	49185
PSMC2	140	IP100021435.1	48634
PSMC3	141	IP100018398.2	49204
PSMC4	142	IP100020042.2	47366
PSMC5	143	IP100023919.2	45626
PSMC6	144	IP100021926.2	44173
PSMD1	145	IP100015333.1	105866
PSMD11	146	IP100105598.1	47464
PSMD12	147	IP100003569.1	52904
PSMD13	148	IP100003570.1	42945
PSMD2	149	IP100012268.1	100200
PSMD3	150	IP100011603.2	60978
PSMD4	151	IP100022694.1	40737
RAB-18	198	IP100014577.1	22977
Rab3 GTPase-activating protein, non-catalytic subunit	199	IP100018280.3	155985
Reelin	89	IP100021018.1	388402
REP8 protein	181	IP100010353.1	30541
REST corepressor	239	IP100008531.1	53028
Retinal short-chain dehydrogenase/reductase retSDR2	183	IP100008260.1	32964

RING finger protein 5	182	IP100012608.1	19881
RNB6	40	IP100008862.1	44792
RPGR-interacting protein 1	88	IP100044777.1	103123
S-100 alpha	230	IP100010824.1	10415
S-100 beta	231	IP100023009.1	10582
Sambiasin-1	267		26840
Sambiasin-2 (Aph-1b)	208	IP100103233.1	28460
SAP-62	41	IP100017341.2	49256
Seipin	261	IP100074114.1	51287
SEL-1 homologue	260	IP100002790.1	88755
Serine/threonine protein phosphatase 6	90	IP100012970.1	35144
Sideroflexin 1	201	IP100009368.2	35619
Signal transducer and activator of transcription-1	202	IP100030781.1	87335
SMAP-1B	200	IP100072534.1	103077
Sortilin 1	18	IP100016022.1	92100
Sortilin-related receptor 1	91	IP100022608.1	248441
Stearoyl-CoA desaturase	155	IP100100476.1	41523
Sterile alpha and HEAT/Armadillo motif protein	19	IP100007919.1	75337
Sterol O-acetyltransferase 1	203	IP100019898.1	64763
Stromal cell-derived factor 2-like 1	184	IP100106642.2	23511
Synaptogyrin 3	92	IP100013947.1	24555

Syntaxin-1	93	IP100003370.1	33023
Tau	250	IP100025499.1	45850
Thioredoxin domain-containing protein	185	IP100001028.1	32535
TNRC15	223	IP100160501.1	127290
TPST1	224	IP100030106.1	42188
Transcription factor CP2	42	IP100037599.1	57256
Triple functional domain protein (PTPRF interacting)	204	IP100026676.1	324106
Ubiquilin	20	IP100099550.1	62519
Ubiquitin-protein ligase E3-alpha	94	IP100156938.1	83595
Ubiquitin-protein ligase EDD	156	IP100026320.1	309352
UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase 7	265	IP100010104.1	75402
Vacuolar ATP synthase membrane sector associated protein m8-9	205	IP100041030.1	39036
VGF nerve growth factor inducible protein	95	IP100019628.1	67287
Voltage-dependent anion channel 1	186	IP100010430.1	30641
Voltage-dependent anion channel 2	157	IP100019625.1	31595
Voltage-dependent anion channel 3	216	IP100031804.1	30659
Wolframin	158	IP100008711.1	100306
X11beta	96	IP100017817.1	82512
Zinc finger protein 198	97	IP100032608.2	154911
Zinc finger protein 277	43	IP100016686.1	51615
ZIP kinase	225	IP100015213.1	52536

TABLE 3

## BIOCHEMICAL ACTIVITIES OF THE COMPLEXES OF THE INVENTION

Name of complex	Biochemical Activity
Presenilin 1 complex	Gamma-secretase activity
Sambiasin complex	Gamma-secretase activity
Presenilin 2 complex	Gamma-secretase activity
Nicastrin complex	Gamma-secretase activity and assembly (trafficking)
Aph-1a complex	Gamma-secretase activity and assembly (trafficking)
Aph-1b complex	Gamma-secretase activity and assembly (trafficking)
Pen-2 complex	Gamma-secretase activity and assembly (trafficking)
BACE1 D215N complex	Beta-secretase activity
APP complex	Signalling activity (regulator of transcription)
APP695SW complex	Signalling activity (regulator of transcription)
APP-C99 complex	Signalling activity (regulator of transcription)
Tau complex	Regulator of microtubules and vesicle transport along microtubules
X11beta complex	Regulator of APP processing and APP function
Fe65 complex	Regulator of APP processing and APP function

Calsenilin complex

Regulator of transcription

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

## REFERENCES

1. Kovacs, D.M., et al., *Alzheimer-associated presenilins 1 and 2: neuronal expression in brain and localization to intracellular membranes in mammalian cells*. *Nat Med*, 1996. 2(2): p. 224-9.
2. De Strooper, B., et al., *Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein*. *Nature*, 1998. 391(6665): p. 387-90.
3. De Strooper, B., et al., *A presenilin-1-dependent gamma-secretase-like protease mediates release of Notch intracellular domain*. *Nature*, 1999. 398(6727): p. 518-22.
4. Ray, W.J., et al., *Evidence for a physical interaction between presenilin and notch*. *Proc Natl Acad Sci USA*, 1999. 96(6): p. 3263-8.
5. Georgakopoulos, A., et al., *Presenilin-1 forms complexes with the cadherin/catenin cell-cell adhesion system and is recruited to intercellular and synaptic contacts*. *Mol Cell*, 1999. 4(6): p. 893-902.
6. Zhang, Z., et al., *Destabilization of beta-catenin by mutations in presenilin-1 potentiates neuronal apoptosis*. *Nature*, 1998. 395(6703): p. 698-702.
7. Yu, G., et al., *The presenilin 1 protein is a component of a high molecular weight intracellular complex that contains beta-catenin*. *J Biol Chem*, 1998. 273(26): p. 16470-5.
8. Zhou, J., et al., *Presenilin 1 interaction in the brain with a novel member of the Armadillo family*. *Neuroreport*, 1997. 8(8): p. 2085-90.
9. Levesque, G., et al., *Presenilins interact with armadillo proteins including neural-specific plakophilin-related protein and beta-catenin*. *J Neurochem*, 1999. 72(3): p. 999-1008.
10. Tanahashi, H. and T. Tabira, *Isolation of human delta-catenin and its binding specificity with presenilin 1*. *Neuroreport*, 1999. 10(3): p. 563-8.
11. Xia, W., et al., *Interaction between amyloid precursor protein and presenilins in mammalian cells: implications for the pathogenesis of Alzheimer disease*. *Proc Natl Acad Sci USA*, 1997. 94(15): p. 8208-13.
12. Yu, G., et al., *Nicastrin modulates presenilin-mediated notch/glp-1 signal transduction and betaAPP processing*. *Nature*, 2000. 407(6800): p. 48-54.
13. Francis, R., et al., *aph-1 and pen-2 are required for Notch pathway signaling, gamma-secretase cleavage of betaAPP, and presenilin protein accumulation*. *Dev Cell*, 2002. 3(1): p. 85-97.
14. Goutte, C., et al., *APH-1 is a multipass membrane protein essential for the Notch signaling pathway in *Caenorhabditis elegans* embryos*. *Proc Natl Acad Sci U S A*, 2002. 99(2): p. 775-9.
15. Kopan, R. and A. Goate, *A common enzyme connects notch signaling and Alzheimer's disease*. *Genes Dev*, 2000. 14(22): p. 2799-806.

16. Esler, W.P., et al., *Activity-dependent isolation of the presenilin- gamma -secretase complex reveals nicastrin and a gamma substrate*. Proc Natl Acad Sci U S A, 2002. 99(5): p. 2720-5.
17. Citron, M., et al., *Mutant presenilins of Alzheimer's disease increase production of 42-residue amyloid beta-protein in both transfected cells and transgenic mice*. Nat Med, 1997. 3(1): p. 67-72.
18. Jarrett, J.T., E.P. Berger, and P.T. Lansbury, Jr., *The carboxy terminus of the beta amyloid protein is critical for the seeding of amyloid formation: implications for the pathogenesis of Alzheimer's disease*. Biochemistry, 1993. 32(18): p. 4693-7.
19. Satoh, J. and Y. Kuroda, *Nicastrin, a key regulator of presenilin function, is expressed constitutively in human neural cell lines*. Neuropathology, 2001. 21(2): p. 115-22.
20. Chen, F., et al., *Nicastrin binds to membrane-tethered Notch*. Nat Cell Biol, 2001. 3(8): p. 751-4.
21. Lopez-Schier, H. and D. St Johnston, *Drosophila nicastrin is essential for the intramembranous cleavage of notch*. Dev Cell, 2002. 2(1): p. 79-89.
22. Chung, H.M. and G. Struhl, *Nicastrin is required for Presenilin-mediated transmembrane cleavage in Drosophila*. Nat Cell Biol, 2001. 3(12): p. 1129-32.
23. Hu, Y., Y. Ye, and M.E. Fortini, *Nicastrin is required for gamma-secretase cleavage of the Drosophila Notch receptor*. Dev Cell, 2002. 2(1): p. 69-78.
24. Lee, S.F., et al., *Mammalian APh-1 interacts with presenilin and nicastrin, and is required for intramembrane proteolysis of APP and Notch*. J Biol Chem, 2002. 277: p. 23.
25. Leem, J.Y., et al., *Presenilin 1 is required for maturation and cell surface accumulation of nicastrin*. J Biol Chem, 2002. 277: p. 19236-40.
26. Tomita, T., et al., *Complex N-glycosylated form of nicastrin is stabilized and selectively bound to presenilin fragments*. FEBS Lett, 2002. 520(1-3): p. 117-21.
27. Edbauer, D., et al., *Presenilin and nicastrin regulate each other and determine amyloid beta-peptide production via complex formation*. Proc Natl Acad Sci U S A, 2002. 99(13): p. 8666-71.
28. Yang, D.S., et al., *Mature glycosylation and trafficking of nicastrin modulate its binding to presenilins*. J Biol Chem, 2002. 277(31): p. 28135-42.
29. Kimberly, W.T., et al., *Complex N-linked glycosylated Nicastrin associates with active gamma -secretase and undergoes tight cellular regulation*. J Biol Chem, 2002. 277: p. 35113-7.
30. Steiner, H., et al., *PEN-2 is an integral component of the gamma -secretase complex required for coordinated expression of presenilin and nicastrin*. J Biol Chem, 2002. 277: p. 39062-5.

31. Vassar, R., et al., *Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE*. Science, 1999. **286**(5440): p. 735-41.
32. Roberds, S.L., et al., *BACE knockout mice are healthy despite lacking the primary beta-secretase activity in brain: implications for Alzheimer's disease therapeutics*. Hum Mol Genet, 2001. **10**(12): p. 1317-24.
33. Huse, J.T., et al., *Maturation and endosomal targeting of beta-site amyloid precursor protein-cleaving enzyme. The Alzheimer's disease beta-secretase*. J Biol Chem, 2000. **275**(43): p. 33729-37.
34. Bennett, B.D., et al., *A furin-like convertase mediates propeptide cleavage of BACE, the Alzheimer's beta -secretase*. J Biol Chem, 2000. **275**(48): p. 37712-7.
35. Masters, C.L., et al., *Amyloid plaque core protein in Alzheimer disease and Down syndrome*. Proc Natl Acad Sci U S A, 1985. **82**(12): p. 4245-9.
36. Van Nostrand, W.E., et al., *Protease nexin-II, a potent antichymotrypsin, shows identity to amyloid beta-protein precursor*. Nature, 1989. **341**(6242): p. 546-9.
37. Multhaup, G., et al., *The amyloid precursor protein of Alzheimer's disease in the reduction of copper(II) to copper(I)*. Science, 1996. **271**(5254): p. 1406-9.
38. Yan, S.D., et al., *RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease*. Nature, 1996. **382**(6593): p. 685-91.
39. Kaneko, I., et al., *Suppression of mitochondrial succinate dehydrogenase, a primary target of beta-amyloid, and its derivative racemized at Ser residue*. J Neurochem, 1995. **65**(6): p. 2585-93.
40. Bertram, L. and R.E. Tanzi, *Dancing in the dark? The status of late-onset Alzheimer's disease genetics*. J Mol Neurosci, 2001. **17**(2): p. 127-36.
41. De Jonghe, C., et al., *Flemish and Dutch mutations in amyloid beta precursor protein have different effects on amyloid beta secretion*. Neurobiol Dis, 1998. **5**(4): p. 281-6.
42. Cao, X. and T.C. Sudhof, *A transcriptionally [correction of transcriptively] active complex of APP with Fe65 and histone acetyltransferase Tip60*. Science, 2001. **293**(5527): p. 115-20.
43. Baek, S.H., et al., *Exchange of N-CoR corepressor and Tip60 coactivator complexes links gene expression by NF-kappaB and beta-amyloid precursor protein*. Cell, 2002. **110**(1): p. 55-67.
44. Kinoshita, A., et al., *The gamma secretase-generated carboxyl-terminal domain of the amyloid precursor protein induces apoptosis via Tip60 in H4 cells*. J Biol Chem, 2002. **277**(32): p. 28530-6.
45. Weggen, S., et al., *A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity*. Nature, 2001. **414**(6860): p. 212-6.

46. Buxbaum, J.D., et al., *Calsenilin: a calcium-binding protein that interacts with the presenilins and regulates the levels of a presenilin fragment*. Nat Med, 1998. 4(10): p. 1177-81.
47. An, W.F., et al., *Modulation of A-type potassium channels by a family of calcium sensors*. Nature, 2000. 403(6769): p. 553-6.
48. Cheng, H.Y., et al., *DREAM is a critical transcriptional repressor for pain modulation*. Cell, 2002. 108(1): p. 31-43.
49. Alonso, A.C., I. Grundke-Iqbal, and K. Iqbal, *Alzheimer's disease hyperphosphorylated tau sequesters normal tau into tangles of filaments and disassembles microtubules*. Nat Med, 1996. 2(7): p. 783-7.
50. McLoughlin, D.M. and C.C. Miller, *The intracellular cytoplasmic domain of the Alzheimer's disease amyloid precursor protein interacts with phosphotyrosine-binding domain proteins in the yeast two-hybrid system*. FEBS Lett, 1996. 397(2-3): p. 197-200.
51. Scheinfeld, M.H., et al., *Processing of beta -Amyloid Precursor Like Protein-1 and -2 by hgamma -secretase regulates transcription*. J Biol Chem, 2002.
52. Sabo, S.L., et al., *Regulation of beta-amyloid secretion by FE65, an amyloid protein precursor-binding protein*. J Biol Chem, 1999. 274(12): p. 7952-7.
53. Kimberly, W.T., et al., *The intracellular domain of the beta-amyloid precursor protein is stabilized by Fe65 and translocates to the nucleus in a notch-like manner*. J Biol Chem, 2001. 276(43): p. 40288-92.
54. Zambrano, N., et al., *The Fe65 adaptor protein interacts through its PID1 domain with the transcription factor CP2/LSF/LBP1*. J Biol Chem, 1998. 273(32): p. 20128-33.
55. Trommsdorff, M., et al., *Interaction of cytosolic adaptor proteins with neuronal apolipoprotein E receptors and the amyloid precursor protein*. J Biol Chem, 1998. 273(50): p. 33556-60.
56. Bruni, P., et al., *Fe65, a ligand of the Alzheimer's beta-amyloid precursor protein, blocks cell cycle progression by down-regulating thymidylate synthase expression*. J Biol Chem, 2002. 277(38): p. 35481-8.
57. Biederer, T. and T.C. Sudhof, *Mints as adaptors. Direct binding to neurexins and recruitment of munc18*. J Biol Chem, 2000. 275(51): p. 39803-6.
58. Ho, C.S., et al., *Synergistic effects of Munc18a and X11 proteins on amyloid precursor protein metabolism*. J Biol Chem, 2002. 277(30): p. 27021-8.
59. Sastre, M., R.S. Turner, and E. Levy, *X11 interaction with beta-amyloid precursor protein modulates its cellular stabilization and reduces amyloid beta-protein secretion*. J Biol Chem, 1998. 273(35): p. 22351-7.
60. Lee, D.S., et al., *Regulation of X11L-dependent amyloid precursor protein metabolism by XB51, a novel X11L-binding protein*. J Biol Chem, 2000. 275(30): p. 23134-8.

61. Hase, M., et al., *Expression and characterization of the Drosophila X11-like/Mint protein during neural development*. J Neurochem, 2002. 81(6): p. 1223-32.
62. Tomita, S., et al., *PDZ domain-dependent suppression of NF-kappaB/p65-induced Abeta42 production by a neuron-specific X11-like protein*. J Biol Chem, 2000. 275(17): p. 13056-60.

CLAIMS

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein, which first protein is selected from the group of proteins in table 1, fourth column of a given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said protein, the variant being, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and
  - (b) at least one second protein, which second protein is selected from the group of proteins in table 1, fifth column of said given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said second protein, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
2. A protein complex comprising a first protein selected from the proteins listed in table 1, second column of a given complex or a homologue or variant thereof, or a functionally active fragment or functionally active derivative of said first protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said first protein under low stringency conditions, and at least one second protein selected from the group of proteins in table 1, fifth column of a given complex, or a variant or homologue thereof, or a functionally active fragment or a functionally active derivative of said second protein, the variant of said second protein being encoded by a nucleic acid that hybridizes to the nucleic acid of said second protein under low-stringency conditions, and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH

7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

3. A protein complex comprising all proteins selected from the proteins in table 1, third column of a given complex or at least one protein being a homologue thereof, or a variant thereof or functionally active fragment or functionally active derivative of said protein, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low stringency conditions;  
wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
4. A protein complex that comprises all proteins as listed in table 1, third column for a given complex or at least one protein being a homologue or a variant thereof, or a functionally active fragment or a functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins under low stringency conditions, except at least one protein of the proteins listed in table 5, third column, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C, with the proviso that the complex comprises at least one protein selected from table 1, fifth column of a given complex.

5. The complex of any of claims 1 - 4 comprising at least one functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein.
6. The complex of claim 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of claims 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of claims 1 - 7 that is involved in at least one biochemical activity as stated in table 3.
9. A process for preparing a complex of any of claims 1 - 8 and optionally the components thereof comprising the following steps:  
expressing a protein of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the protein, preferably the tagged protein, and optionally disassociating the protein complex and isolating the individual complex members.
10. The process according to claim 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of claims 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of a protein complex obtainable by a process according to any of claims 9 - 11.
13. Protein selected from the group of proteins in table 1, sixth column of a given complex or a homologue or a variant of thereof, or a functionally active fragment or a

functionally active derivative of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to claim 13.
15. Construct, preferably a vector construct, comprising
  - (a) a nucleic acid according to claim 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
  - (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, at least one of said proteins being selected from the first group of proteins according to claim 1 (a) and at least one of said proteins, being selected from the second group of proteins according to claim 1 (b) or
  - (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to claim 1.
16. Host cell, containing a vector comprising at least one nucleic acid of claim 14 and /or a construct of claim 15 or containing several vectors each comprising at least one nucleic acid encoding at least one protein selected from the first group of proteins according to claim 1 (a) and at least one nucleic acid encoding at least one protein selected from the second group of proteins according to claim 1 (b).
17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of

claims 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody containing the binding domain thereof which binds to any of the proteins of the group of proteins according to claim 13.

18. A kit comprising in one or more containers:

- (a) the complex of any of claims 1 - 8 and/or the proteins of claim 13 and/or
- (b) an antibody according to claim 17 and/or
- (c) a nucleic acid encoding a protein of the complex of any of claims 1 - 8 and/or a protein of claim 13 and/or
- (d) cells expressing the complex of any of claims 1 - 8 and/or a protein of claim 13 and, optionally,
- (e) further components such as reagents, buffers and working instructions.

19. The kit according to claim 18 for processing a substrate of a complex of any one of claims 1 - 8.

20. The kit according to claim 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

21. Array, preferably a microarray, in which at least a complex according to any of claims 1 - 8 and/or at least one protein according to claim 13 and/or at least one antibody according to claim 17 is attached to a solid carrier.

22. A process for modifying a substrate of a complex of any one of claims 1 - 8 comprising the step of bringing into contact a complex of any of claims 1 - 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of claims 1 - 8 and/or a protein according to claim 13.

24. A pharmaceutical composition according to claim 23 for the treatment of diseases and disorders, preferentially for diseases or disorders such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
25. A method for screening for a molecule that binds to a complex of any one of claims 1 - 8 and/or a protein of claim 13, comprising the following steps:
- (a) exposing said complex or protein, or a cell or organism containing said complex or said protein, to one or more candidate molecules; and
  - (b) determining whether said candidate molecule is bound to the complex or protein.
26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of claims 1 - 8 comprising the steps of:
- (a) exposing said complex, or a cell or organism containing said complex to one or more candidate molecules; and
  - (b) determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent upon the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity, or composition of said complex.
27. The method of claim 26, wherein the amount of said complex is determined.
28. The method of claim 26, wherein the activity of said complex is determined.

29. The method of claim 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
30. The method of claim 26, wherein the amount of the individual protein components of said complex is determined.
31. The method of claim 30, wherein said determining step comprises determining whether any of the proteins listed in table 1, third column of said complex, or a functionally active fragment or a functionally active derivative thereof, or a variant or a homologue thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low-stringency conditions, is present in the complex.
32. The method of any of claims 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder, preferentially of a disease or disorder selected from the diseases or disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of claims 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
34. A method for the production of a pharmaceutical composition comprising carrying out the method of claims 26 - 31 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, component disposition of, or intracellular localization of the complex of any one of the claims 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicated the presence in the subject of the disease or disorder or predisposition in the subject.
36. The method of claim 35, wherein the amount of said complex is determined.
37. The method of claim 35, wherein the activity of said complex is determined.
38. The method of claim 37, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
39. The method of claim 35, wherein the amount of the individual protein components of said complex is determined.
40. The method of claim 39, wherein said determining step comprises determining whether any of the proteins according to claim 13 is present in the complex.
41. The complex of any one of claims 1 - 8, or a protein of claim 13 or an antibody or fragment thereof of claim 17, for use in a method of diagnosing a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity of, component composition of or intracellular localization of, the complex of any one of claims 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, activity of, or protein composition of, said complex.
43. The method according to claim 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.
44. The method according to claim 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.
45. Complex of claims 1 - 8 and/or a protein as listed in table 1, fifth column of said complex as a target for an active agent of a pharmaceutical, preferably a drug target, in the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as a neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

ABSTRACT

The present invention relates to protein complexes of the beta-amyloid precursor protein (APP) processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the complexes of the APP processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

SEQUENCES

SEQ ID No:1

MTAVHAGNINFKWDPKSLEIRTLAVERLLEPLVTQVTTLVNTNSKGPSNKKRGRSKKAH  
 VLAASVEQATENFLEKGDKIAKESQFLKEELVAAVEDVRKQGDLMKAAAGEFADDDPCS  
 SVKRGNMVRAARALLSAVTRLLILADMADVYKLLVQLKVVEDGILKLRNAGNEQDLGIQY  
 KALKPEVDKLNIMAAKRQQELKDVGHRDQMAAARGILQKNVPILYTASQACQLQHPDVAA  
 YKANRDLIYKQLQQA VTGISNAAQATASDDASQHQQGGGGGELAYALNNFDKQIIVDPLS  
 FSEERFRPSLEERLESIIISGAALMADSSCTRDDRERIVAECNAVRQALQDLLSEYMGN  
 AGRKERSDALNSAIDKMTKKTRDLRRQLRKAVMDHVSDSFLETNVPLLVLEAAKNGNE  
 KEVKEYAQVFREHANKLIEVANLACISISNNEEGVKLVMSASQLEALCPQVINAALALAA  
 KPQSKLAQENMDLFKEQWEKQVRVLTDAVDDITSIDDFLAVSENHILEDVNKCVIALQEK  
 DVDGLDRTAGAIRGRAARVIHVVTSEMDNYEPGVYTEKVLKLLSNTVMPRFTEQVE  
 AAVEALSSDPAQPMDENEFIDASRLVYDGIRDIRKAVLMIRTPEELDDSDFETEDFDVRS  
 RTSVQTEDDQLIAGQSARAIMAQLPQEQKAKIAEQVASFQEEKSKLDAEVSKWDDSGN  
 DIIVLAKQMCMIMMEMTDFTRGKGPLKNTSDVISAACKIAEAGSRMDKLGRTIADHCPDS  
 ACKQDLLAYLQRIALYCHQLNICKVKAQVQNLGGELVVGVSAMS LIQAAKNLMNAV  
 VQTVKASYVASTKYQKSQGMASLNLPAVSWKMKAPEKKPLVKREKQDETQTKIKRASQ  
 KKHVNPVQALSEFKAMDSI

SEQ ID No:2

MGAAVFFGCTFVAFGPAFALFLITVAGDPLRVILVAGAFFWLVSLLLASVWVWVILVHVTD  
 RSDARLQYGLLIFGAAVSVLLQEVFRFAYYKLLKKADEGLASLSEDGRSPISIRQMAYVS  
 GLSFGIISGVFSVINILADALGPGVVG IHG DSPYYFLTSAFLTAAILLHTFWGVVFFDACE  
 RRRYWALGLVVGSHLLTSGLTFLNPWYEASLLPIYAVTVSMGLWAFITAGGSLRSIQRS  
 LLCRRQEDSRVMVYSALRIPPED

SEQ ID No:3

MNIFDRKINF DALLKFSHITPSTQQHLKKVYASFALCMFVAAAGAYVH MVTHFIQAGLLS  
 ALGSLILMIWLMATPHSHETEQRGLLAGFAFLTGVGLGPALEFCIAVNPSILPTAFMG T  
 AMIFTCFTLSALYARRRSYLFLGGILMSALSLLLLSSLG NVFFGSIWLFQANLYVGLVVMC  
 GFVLFDTQLIIEKAEHGDQDYIWHCIDLFLDFITVFRKLMMILAMNEKDKKKEKK

SEQ ID No:4

MATQADLMELDMAMEPDRKAAVSHWQQQSYLDSGIHSGATTTAPSLSGKGNPEEEDV  
DTSQVLYEWEQGFSSQFTQEQQVADIDGQYAMTRAQRVRAAMFPETLDEGMQIPSTQF  
DAAHPTNVQRLAEP SQMLKHAVVNLINYQDDAELATRAIPELTKLLNDEDQVVVNKAAV  
MVHQLSKKEASRHAIMRSPQMVSIVRTMQNTNDVETARCTAGTLHNLSHHREGLLAIF  
KSGGIPALVKMLGSPVDSVLFYAITTLHNLLLHQEGAKMAVRLAGGLQKMVALLNKTNV  
KFLAITTDCLQILAYGNQESKLIILASGGPQALVNIMRTYTYEKLLWTTSRVLKVLVSVCSS  
NKPAIVEAGGMQALGLHLTDPSQRLVQNCLWTLRNLSDAATKQEGMEGLLGTLVQLLG  
SDDINVVTCAAGILSNLTCNNYKNKMMVCQVGGIEALVRTVLRAGDREDITEPAICALRH  
LTSRHQEAEMAQNAVRLHYGLPVVVKLLHPPSHWPLIKATVGLIRNLALCPANHAPLRE  
QGAIPRLVQLLVRAHQDTQRRTSMGGTQQQFVEGV RMEEIVEGCTGALHILARDVHNR  
IVIRGLNTIPLFVQLLYSPIENIQRVAAGVLCELAQDKEAAEAIEAEGATAPL TELLHSRNE  
GVATYAAAVLFRMSEDKPQDYKKRLSVELTSSLFRTEPMAWNETADLGLDIGAQGEPL  
GYRQDDPSYRSFHSGGYGQDALGMDPMMHEHEMGGHHPGADYPVDGLPDLGHAQDL  
MDGLPPGDSNQLAWFDTDL

SEQ ID No:5

MPSKSLVMEYLAHPSTLGLAVGVACGMCLGWSLRVCFGMLPKSKTSKTHTDTESEASI  
LGDSGEYKMILVVRNDLKMKGKGVAAQCSHAAVSAYKQIQRRNPEMLKQWEYCGQPK  
VVVKAPDEETLIALLAHAKMLGLTVSLIQDAGRTQIAPGSQTVLGIGPGPADLIDKVTGHL  
KLY

SEQ ID No:6

MKENYCLQAALVCLGMLCHSHAFAPERRGHLRPSFHGHHEKGKEGQVLQRSKRGWV  
WNQFFVIEEYTGPDVVLVGR LHSDIDSGDGNIKYILSGEGAGTIFVIDDKSGNIHATKTLD  
REERAQYTLMAQAVDRDTRNRPLEPPSEFIVKVQDINDNPPEFLHETYHANVPERSNVGT  
SVIQVTASDADDPTYGNSAKLVYSILEGQPYFSVEAQTGIIRTALPNMDREAKEEYHVVI  
QAKDMGGHMGGLSGTTKVITITLTDVNDNPPKFPQRLYQMSVSEAAVPGEVGRVKAK  
DPDIGENGLVTYNIVDGDGMESFEITTDYETQEGVIKLPVDFETERAYSLKVEAANVH  
IDPKFISNGPFKDTVTVKISVEDADEPPMFLAPSYIHEVQENAAAGTVVGRVHAKDPDAA  
NSPIRYSIDRHTDLDRFFTINPEDGFIKTTKPLDREETAWLNITVFAAEIHNRHQEAQVPV  
AIRVLDVNDNAPKFAAPYEGFICESDQTKPLSNQPIVTISADDKDDTANGPRFIFSLPPEII  
HNPNTVTRDNRDNTAGVYARRGGFSRQKQDLYLLPIVISDGGIPPMSSNTLTIKVCGC  
DVNGALLSCNAEAYILNAGLSTGALIAILACIVILLVIVVLFVTLRRQKKEPLIVFEEEDVRE  
NIITYDDEGGGEEDTEAFDIATLQNP DGINGFIPRKDIKPEYQYMPRPGLRPAPNSVDVD

DFINTRIQEADNDPTAPPYDSIQIYGYEGRGSVAGSLSSLESATTDSDLDYDYLQNWGP  
RFKKLADLYGSKDTFDDDS

SEQ ID No:7

QIRSDKDNDIPRYSITGVGADQPPMEVFSIDSMGRMYVTRPMDREEHASYHLRAHAV  
DMNGNKVENPIDLYIYVIDMNDNRPEFINQVYNGSVDEGSKPGTYVMTVTANDADDSTT  
ANGMVRYRIVTQTPQSPSQNMFTINSETGDIVTVAAGLDREKVQQYTIVVQATDMEGNL  
NYGLSNTATAIITVTDVNDNPPEFTASTFAGEVPENRVETVVANLTVMDRDQPHSPNWN  
AVYRIISGDPGSGHFSVRTDPVTNEGMVTVVKAVDYELNRAFMLTVMVSNQAPLASGIQM  
SFQSTAGVTISIMDINEAPYFPSNHKLIRLEEGVPPGTVLTTFSAVDPDRFMQQAVRYSK  
LSDPASWLHINATNGQITTAAVLDRESLYTKNNVYEATFLAADNGIPPASGTGTLQIYLIDI  
NDNAPELLPKEAQICEKPNLNAINITAADADVDPNIGPYVFEARAGLWLNWYCCFAPGDY  
AQLSLRILYLEAGMYDVPIIVTDSGNPPLSNTSIIKVVCPCDDNGDCTTIGAVAAAGLGT  
GAIVAILICILILLTMVLLFVMWMKRREKERHTKQLLIDPEDDVRDNILKYDEEGGGEEDQ  
VRLRPAPASPREAGSHVVXRAADNDPTAPPYDSLLVFDYEGSGSTAGSVSSLNSSSSG  
DQDYDYLDNDWGPRFKKLADMYGGG

SEQ ID No:8

MDDSEVESTASILASVKEQEAQFEKLTRALEEERRHVSAQLERVRVSPQDANPLMANG  
TLTRRHQNGRFVGDADLERQKFSDLKLNQPQDHSLLYSTIPRMQEPGQIVETYTEED  
PEGAMSVVSVETSDDGTTRRTETTVKKVVKTVTTRTVQPVAMGPDGLPVDASSVSNNY  
IQTGLGRDFRKNNGGGPGPYVGQAGTATLPRNFHYPPDGYSRHYEDGYPGGSDNYGSL  
SRVTRIEERYRPSMEGYRAPSQRQDVYGPQPQVRVGGSSVDLHRFHPEPYGLEDDQRS  
MGYDDL DYGMMSDYGTARRTGTPSDPRRRLRSYEDMIGEEVPSDQYYWAPLAQHER  
GSLASLDSLRLKGGPPPNWRQPELPEVIAMLGFRLDVKSNAAYLQHLCYRNDKVKT  
DVRKLKGIPVLVGLLDHPKKEVHLGACGALKNISFGRDQDNKIAIKNCDGVPALVRLLRK  
ARDMDLTEVITGTLWNLSSHDSIKMEIVDHALHALTDEVIIPHSGWEREPNEDCKPRHIE  
WESVLTNTAGCLRVSSERSEARRKLRECDGLVDALIFIVQAEIGQKDSDSL VENCVC  
LLRNLSYQVHREIPQAERYQEAAPNVANNTGPHAASCFGAKKGKGKGPEDPANDTVD  
FPKRTSPARGYELLFQPEVVRIYISLLKESKTPAILEASAGAIQNLCAGRWTYGRYIRSAL  
RQEKALSAIADLLTNEHERVVKAASGALRNLAVDARNKELIGKHAIPNLVKNLPGGQQN  
SSWNFSEDTVISILNTINEVIAENLEAAKKLRETQGIEKLVLINKSGNRSEKEVRAAALVLQ  
TIWGYKELRKPLEKEGWKKSDFQVNLNNASRSQSSHSYDDSTLPLIDRNQKSDNNYST

PNERGDHNRTLDRSGDLGDMEPLKGTTPLMQDEGQESLEEELDVLVLDDDEGGQVSYP  
SMQKI

SEQ ID No:9

MFARKPPGAAPLGAMPVPDQPSSASEKTSSLSPGLNTSNGDGSETETTSAILASVKEQ  
ELQFERLTRELEAERQIVASQLERCKLGSETGSMSSMSSAEEQFQWQSQDQGKDIEDE  
LTTGLELVDSCIRSLQESGILDPQDYSTGERPSLLSQSALQLNSKPEGSFQYPASYHSN  
QTLALGETTPSQLPARGTQARATGQSFSQGTTSRAGHLAGPEPAPPPPPPPREPFPAS  
LGSFHLDPDAPPAALYSSSTLPAPPRGGSPLAAPQGGSPTKLQRGGSAPEGAT  
YAAPRGSSPKQSPSRLAKSYSTSSPINIVVSSAGLSPIRVTSPTTVQSTISSSPIHQLSSTI  
GTATLSPTKRLVHASEQYSKHSQELYATATLQRPGLAAGSRASYSSQHGHLPGLR  
ALQSPEHHIDPIYEVRYQKPPMRSLSQSQGVPLPPAHTGTYRTSTAPSSPGVDSVPLQ  
RTGSQHGPQNAATFQRASYAAGPASNYADPYRQLQYCPSVESPYSKSGPALPPEG  
TLARSPSIDSIQKDPREFGWRDPELPEVIQMLQHGFPSVQSNAAAYLQHLGFGDNKIKA  
EIRRQGGIQLLDLLDHRMTEVHRSACGALRNLYGKANDDNKIALKNCGGIPALVRLLR  
KTTDLIELVLTGVLWNLSSCDALKMPIIQDALAVLTNAVIPHSGWENSPLQDDRKIQLH  
SSQVLRNATGCLRNVSPPGEEARRRMRECDGLTDALLYVIQSALGSSEIDSKTVENCV  
CILRNLSYRLAAETSQGGQHMGTDEL DGLLCEANGKDAESSGCWGKKKKKKKSQDQ  
WDGVGPLPDCAEPPKGIQMLWHPISVKPYLTLLSECSNPDTLEGAAGALQNLAAAGSWK  
WSVYIRAAVRKEKGRPILVELLRIDNDRVACAVATALRNMALDVRNKEKIGKYAMRDLVH  
RLPGGNNNSNTASKAMSDDTVTAVCCTLHEVITKNMENAKALRDAGGIEKLVGISKSKG  
DKHSPKVKAASQVLNSMWQYRDLRSYKKGWSQYHFVASSSTIERDRQRPYSSSR  
TPSISPVVSPNNRSASAPASPREMISLKERKTDYECTGSNATYHGAKGEHTSRK DAM  
TAQNTGISTLYRNSYGAPAEDIKHNQVSAQPVPQEPSRKDYETYQPFQNSTRYNDESF  
FEDQVHHRPPASEYTMHLGLKSTGNYVDFYSAARPYSELNYETSHYPASPD SWV

SEQ ID No:10

MRLTRCQAALAAAITLNLVLFYVSWLQHQPNSRARGPRRASAAGPRVTVLVREFEA  
FDNAVPELVDSFLQQDPAQPVVVAADTLPPPLALPRIPNVRLALLQPALDRPAAASRP  
ETYVATEFVALVPDGAARAEAPGLLERMVEALRAGSARLVAAPVATANPARCLALNVSLR  
EWTARYGAAPAAPRCDALDGDVLLRARDLNL SAPLARPVGTSFLQTALRGWAVQ  
LLDLTFAAARQPPLATAHARWKAEREGRARRAALLRALGIRLVSWEGGRLEWFGCNKE  
TTRCFGTVVGDTPAYLYEERWTPPCCLRALRETARYVVGVLAAAGVRYWLEGGSSLLGA  
ARHGDIIPWDYDVLGIYLEDVGNCEQLRGAEAGSVVDERGFVWEKAVEGDFFRVQYS

ESNHLHVDLWPFYPRNGVMTKDTWLDHRQDVEFPEHFLQPLVPLPFAGFVAQAPNNY  
RRFLELKFGPGVIENPQYPNPALLSLTGSG

SEQ ID No:11

MPATLLRAVARSHHILSKAHQCRRIGHLMLKPLKEFENTTCSTLTIRQSLDLFLPKTAS  
GLNKSQILEMNQKKS DTSMLSPLNAARCQDEKAHLPTMKSFGTHRRVTHKPNLLGSKW  
FIKILKRHFSSVSMETFVPKQDFPQVKRPLKASRTRQPSRTNLPVLSVNEDPMHCTAFA  
TADEYHLGNLSQDLASHGYVEVTS LPRDAANILVMGVENSAKEGDPGTIFFFREGAAVF  
WNVKDKTMKHVMKVLEKHEIQPYEIALVHWENEELNYIKIEGQSKLHRGEIKLNSELDLD  
DAILEKFAFSNALCLSVKLAIWEASLDKFIESIQSIPEALKAGKKVKSHEEVMQKIGELFA  
LRHRINLSSDFLITPDFYWDRENLEGLYDKTCQFLSIGRRVKVMNEKLQHCMELTDLMR  
NHLNEKRALRLEWMIVILITIEVMFELGRVFF

SEQ ID No:12

EVMNLMEQPIKVTEWQQTYTYDSGIHSGANTCVPSVSSKGIMEEDEACGRQYTLKKT  
TYTQGVPPSQGDLEYQMSTTARAKRVREAMCPGVSGEGQLALLATQVEGQATNLQRL  
AEPSQLLKSAIVHLINYQDDAELVTRALPELT KLLNDEDPVVVTKAAMIVNQLSKKEASR  
RALMGSPQLVAAVVRTMQNTSDLDTARCTTSILHNLSSHREGLLAIFKSGGIPALVRMLS  
SPVESVLFYAITTLHNLLLYQEGAKMACAGRRAQKMVPLLNNPKFLAITTDCLQLLAY  
GNQESKLILANGGPQALVQIMRNYSYEKLLWTTSRVLKVL SVCPSNKP AIVEAGGMQA  
LGKHLTSNSPRLVQNCLWTLRNLSDVATKQEGLESVLKILVNQLSVDDVNVLT CATGTL  
SNLTCNNSKNKTLVTQNSGVEALIHAILRAGDKDDITEPAVCALRHLSRHP EAEQAQN  
SVRLNYGIPAIVKLLNQPNQWPLVKATIGLIRNLALCPANHAPLQEA AVIPRLVQLLVKAH  
QDAQRHVAAGTQQPYTDGVRMEEIVEGCTGALHILARDPMNRMEIFRLNTIPLFVQLLY  
SSVENIQRVAAGVLCELAQDKEADAIDAEGASAPLMELLHSRNEG TATYAAAVLFRISE  
DKNPDYRKRVSVELTNSL FKHDPA AWEAAQSMIPINEPYGDDMDATYRPMYSSDVPLD  
PLEMHMDMDGDYPIDTYS DGLRPPYPTADHMLA

SEQ ID No:13

MTLIEGVGDEVTVLFSVLACLLVLALAWVSTHTAEGGDPLPQPSGTPTPSQPSAAMAAT  
DSMRGEAPGAETPSLRHRGQAAQPEPSTGFTATPPAPDSPQEPLVRLKFLNDSEQVA  
RAWPHDTIGSLKRTQFPGREQQVRLIYQGQLLGDDTQTLGSLHLPPNCVLHCHVSTRV  
GPPNPCCPPGSEPGPSGLEIGSLLLPLLLLLLLLLLWYCQIQYRPFPLTATLGLAGFTLLL  
SLLAFAMYRP

SEQ ID No:14

MATAGGGSGADPGSRGLLRLLSFCVLLAGLCRGNSVERKIYIPLNKTAPCVRLLNATHQI  
GCQSSISGDTGVIHVVEKEEDLQWVLT DGP NPPY MV LLESKHFT RD LMEK LKGRTSRIA  
GLAVSLTKPSPASGFSPSVQCPNDGFGVYSNSYGPEFAHCREIQWNSLGNGLAYEDFS  
FPIFLLDENETKVIKQCYQDHNLSQNGSAPT FPLCAMQLFSHMHAVISTATCMRRSSIQ  
STFSINPEIVCDPLSDYNVWSMLKPINTTGTLKPDDR VVAATRLDSRSFFWNVAPGAE  
SAVASFVTQLAAAEALQKAPDVTTLP RNVMFVFFQGETFDYIGSSRMVYDMEKGKFPV  
QLENVDSFVELGQVALRTSLELWMHTDPVSQKNESVRNQVEDLLATLEKSGAGVPAVI  
LRRPNQSQPLPPSSLQRFLRARNISGVVLADHSGAFHNKYYQSIYDTAENINVSYPEWL  
SPEEDLN FVTD TAKALADVATV LGRALYELAGGTNFSDTVQADPQTVTRLLYGFLIKAN  
NSWFQSILRQDLRSYLG DGPLQH YIAVSSPTNTTYV VQYALANLT GTV VNL TREQCQDP  
SKVPSENK DLYEYSWVQG PLHSNETDRLPRCVRSTARLARALSPAFELSQWSSTEYST  
WTESRWKDIRARIFLIASKELELITLVGFGILIFSLIVTYCINAKADVLFIAPREPGAVSY

SEQ ID No:15

MNLERSNEEKLNLCKRYLGGFAFLPFLWL VNIFWFFREAF LVPAYTEQS QIKGYVWR  
SAVGFLFWVIVLT SWITIFQIYRPRWGALGDYLSFTIPLGTP

SEQ ID No:16

MPAPEQASLVEEGQPQTRQEAASTGPGMEPETTATTILASVKEQELQFQRLTRELEVE  
RQIVASQLERCRLGAESPSIASTSSTEKSFPWRSTDVPNTGVSKPRVSDAVQPNNYLIR  
TEPEQGTLYSPEQTS LHESEGLGNSRSSTQMNSYSDSGYQEAGSFHNSQNVSKADN  
RQQHSFIGSTNNHVVRNSRAEGQTLVQPSVANRAMRRVSSVPSRAQSPSYVISTGVSP  
SRGSLRTSLGSGFGSPSVTDPRPLNPSAYSSTTLPAARAASPYSQRPASPTAIRRIGSV  
TSRQTSNPNGPTPQYQTTARVGSPLTLTDAQTRVASPSQGQVGSSSPKRSGMTAVPQ  
HLGPSLQRTVHDMEQFGQQQYDIYERMVPPRPDSL TGLRSSYASQHSQLGQDLRSAV  
SPDLHITPIYEGRTYYSPVYRSPNHGTVELQGSQTALYRTGVSGIGNLQRTSSQRSTLT  
YQRNNYALNTTATYAEPYRPIQYRVQECNYNRLQHAVPADDGTT RSPSIDSIQKDPREF  
AWRDPPELPEVIHMLEHQFPSVQANAAAYLQHLCFGDNKVKMEVCRLGGIKHLVDLLDH  
RVLEVQKNACGALRNLVFGKSTDENKIAMKNVGGIPALLRLLRKSIDAEVRELVTGVLW  
NLSSCDAVKMTIIRDALSTLTNTVIVPHSGWNNSSFDH KIKFQTS LVL RNTTGCLRNL  
TSAGEEARKQMRSC EGLVDSL LYVIHTCVNTSDYDSKTVENCVCTLRNLSYRLELEV PQ  
ARLLGLNELDLLGKESPSKDSEPSCWGKKKKKKKRT PQEDQWDGVGPIPGLSKSPK

GVEMLWHPVVKPYLTLLAESSNPATLEGSAGSLQNLSASNWKFAAYIRGGRPKRKGL  
 PILVELLRMDNDRVVSSGATALRNMALDVRNKEKIGKYAMRDLVNRLPGGNGPSVLSD  
 ETMAAICCALHEVTSKNMENAKALADSGGIEKLVNITKGRGDRSSLKVVKAAAQVLNTL  
 WQYRDLRSIYKKDGWNQNHFITPVSTLERDRFKSHPSLSTTNQQMSPIIQSVGSTSSSP  
 ALLGIRDPRSEYDRTQPPMQYYNSQGDATHKGLYPGSSKPSPIYISSYSSPAREQNRRL  
 QHQQLYYSQDDSNRKNFDAYRLYLQSPHSYEDPYFDDRVDHFPASTDYSTQYGLKSTT  
 NYVDFYSTKRPSYRAEQYPGSPDSWVYDQDAQQRNSFFLTLFRLR

SEQ ID No:17

MTELPAPLSYFQNAQMSEDNHLSENTNDNRERQEHNDRRSLGHPEPLSNGRPQGNSR  
 QVVEQDEEEDEELTKYGAKHVIMLFVPVTLCMVVVVATIKSVSFYTRKDGQLIYTPFTE  
 DTETVGQRALHSILNAAIMISVIVVMTILLVVLKYRCYKVIHAWLISSLLLLFFFSFIYLGE  
 VFKTYNVAVDYITVALLIWNLGVVGMISIHWKGPLRLQQAYLIMISALMALVFIKYLPEWT  
 AWLILAVISVYDLVAVLCPKGPLRMLVETAQERNETLFPALIYSSTMVWLVNMAEGDPEA  
 QRRVSKNSKYNAESTERESQDTVAENDDGGFSEWEAQRDShLGPHRSTPESRAAV  
 QELSSSILAGEDPEERGVLGLGDFIFYSVLVGKASATASGDWNTTIACFVAILIGLCLTL  
 LLLAIFKKALPALPISITFGLVFYFATDYLVPFMDQLAFHQFYI

SEQ ID No:18

MERPWGAADGLSRWPHGLGLLLLLQLLPSTLSQDRLDAPPPPAAPLPRWSGPIGVS  
 WGLRAAAAGGAFFPRGGRWRRSAPGEDEECGRVRDFVAKLANNTHQHVFDDLGRSVS  
 LSWVG DSTGVILVLTTFHVPLVIMTFGQSKLYRSEDYGKNFKDITDLINNTFIRTEFGMAI  
 GPENSGKVLTAEVSGGSRGGRIFRSSFDAKNFVQTDLPFHPLTQMMYSPQNSDYLLA  
 LSTENGLWVSKNFGGKWEEIHKAVCLAKWGS DNTIFFTTYANGSCKADLGALELWRTS  
 DLGKSFKTIGVKIYSFGLGGRFLFASVMADKDTTRRIHVSTDQGD TWSMAQLPSVGQE  
 QFYSILAANDDMVFMHVDEPGDTGFGTIFTSDDRGIVYSKSLDRHLYTTTGGETDFTNV  
 TSLRGVYITSVLSEDNSIQTMITFDQGGRWTHLRKPENSECDATAKNKNECSLHIHASY  
 SISQKLNVPMAPLSEPNAVGIIVAHGSGVDAISVMVPDVYISDDGGYSWTKMLEGPHY  
 TILDSGGIIVAIHSSRPINVIKFSTDEGQCWQTYTFTRDPIYFTGLASEPGARSMNISIWG  
 FTESFLT SQWVS YTI DFKDILERNCEEKDYTIWLAHSTDPEDYEDGCILGYKEQFLRLRK  
 SSMCQNGRDYVVTKQPSICLCSLEDFLCDFGYRPPENDSKCQEQLKGHDFCLYG  
 REEHLTTNGYRKIPGDKCQGGVNPVREVKDLKKKCTSNFLSPEKQNSKNSVPIILAIVG  
 LMLVTVVAGVLIVKKYVCGGRFLVHRYSVLQQHAEANGVDGVDALDTASHTNKSGYHD  
 DSDEDLLE

## SEQ ID No:19

MGAVARAHGGLRVARARESVAGGRHRGAGRPGARAAGAAAGLVRAEAGGRRAGRG  
 RRPGRGLPTGGGGGLAAAAGREVAQGLCDAIRLDGGDLRLRLQAPELETRVQAARL  
 LEQILVAENRDRVARIGLGVILNLAKEREPVELARSVAGILEHMFKHSEETCQRLVAAGG  
 LDAVLYWCRRTDPALLRHCALALGNCALHGGQAVQRRMVEKRAAEWLFPLAFSKEDE  
 LLRLHACLAVAVLATNKEVEREVERSGTLALVEPLVASLDPGRFARCLVDASDTSQGRG  
 PDDLQRLVPLLDNRLEAQCIGAFYLCAEAAIKSLQGKTKVFSDIGAIQSLKRLVSYSTNG  
 TKSALAKRALRLLGEEVPRPILPSVPSWKEAEVQTWLQQIGFSKYCESFREQQVDGDL  
 LRLTEELQTDLGMKSGITRKRFRETELKTFANYSTCDRSNLADWLGSLDPRFRQYT  
 YGLVSCGLDRSLLHRVSEQQLLEDGCIHLGVHRARILTAAREMLHSPLPCTGGKPSGDT  
 PDVFISYRRNSGSQLASLLKVHLQLHGFSVFIDVEKLEAGKFEDKLIQSVMGARNFVLVL  
 SPGALDKCMQDHDCKDWVHKEIVTALSCGKNIVPIIDGFEWPEPQVLPEDMQAVLTFN  
 GIKWSHEYQEATIEKIIRFLQGRSSRDSSAGSDTSLEGAAPMGPT

## SEQ ID No:20

MAESGESGGPPGSQDSAAGAEGAGAPAAAASAEPKIMKVTVKTPKEKEEFVAVPENSS  
 VQQFKEEISKRFKSHTDQLVLIFAGKILKDQDTLSQHGHDGLTVHLVIKTQNRPDHSA  
 QQTNTAGSNVTTSSTPNSNSTSGSATSNPFGGLGGLAGLSSLGLNTTNFSELQSQM  
 QRQLLSNPENMMVQIMENPFVQSMLSNPDLMRQLIMANPQMQLIQRNPEISHMLNNPD  
 IMRQTLELARNPAMMQEMMRNQDRALSNISSIPGGYNALRRMYTDIQEPMLSAAQEQF  
 GGNPFASLVSNSTSSGEGSQPSRTENRDPLPNPWAPQTSQSSSASSGTASTVGGTTGS  
 TASGTSGQSTTAPNLVPGVGASMFNTPGMQSLLQQITENPQLMQNMLSAPYMRSM  
 QSLSQNPDLAAQMMLNNPLFAGNPQLQEQRQLPTFLQQMQNPDTLSAMSNPRAM  
 QALLQIQQLQTLATEAPGLIPGFTPGLGALGSTGGSSGTNGSNATPSENTSPTAGTTE  
 PGHQQFIQQLQALAGVNPQLQNPEVRFQQQLEQLSAMGFLNREANLQALATGGDIN  
 AAIERLLGSQPS

## SEQ ID No:21

MDDREDLVYQAKLAEQAERYDEMVESMKKVAGMDVELTVEERNLLSVAYKNVIGARR  
 ASWRIISSIEQKEENKGGEDKLKMIREYRQMVELTELKICCDILDVLDKHLIPAANTGESK  
 VFYYKMKGDYHRYLAEFATGNDRKEAAENSLVAYKAASDIAMTELPPTHPIRLGLALNF  
 SVFYEILNSPDRACRLAKAAFDDAIAELDTLSEESYKDSTLIMQLLRDNLTLWTSDMQG  
 DGEEQNKEALQDVEDENQ

SEQ ID No:22

TMDKSELVQKAKLAEQAERYDDMAAAMKAVTEQGHLSNEERNLLSVAYKNVVGARR  
SSWRVISSIEQKTERNEKKQQMGKEYREKIEAELQDICNDVLELLDKYLIPNATQPESKV  
FYLKMKGDYFRYLSEVASGDNKQTTVSNSQQAYQEAFEISKKEMQPTHPIRLGLALNFS  
VFYYEILNSPEKACSLAKTAFDEAIAELDTLNEESYKDSTLIMQLLRDNLTLWTSENQGD  
EGDAGEGEN

SEQ ID No:23

GDREQLLQRARLAEQAERYDDMASAMKAVTELNEPLSNEDRNLLSVAYKNVVGARRS  
SWRVISSIEQKTMADGNEKKLEKVKAYREKIEKELETVCNVLSLLDKFLIKNCNDFQYE  
SKVFYLYKMKGDYRYLAEVASGEKKNSVVEASEAAYKEAFEISKEQMOPHTPIRLGLAL  
NFSVFYYEIQNAPEQACLLAKQAFDDAIAELDTLNEDSYKDSTLIMQLLRDNLTLWTSDQ  
QDEEAGEGN

SEQ ID No:24

VDREQLVQKARLAEQAERYDDMAAAMKNVTELNEPLSNEERNLLSVAYKNVVGARRS  
SWRVISSIEQKTSADGNEKKIEMVRAYREKIEKELEAVCQDVLSLLDNYLIKNCSETQYE  
SKVFYLYKMKGDYRYLAEVATGEKRATVSESSEKAYSEAHEISKEHMOPHTPIRLGLAL  
NYSVFYYEIQNAPEQACHLAKTAFDDAIAELDTLNEDSYKDSTLIMQLLRDNLTLWTSDQ  
QDDDGEGENN

SEQ ID No:25

MEKTELIQKAKLAEQAERYDDMATCMKAVTEQGAELSNEERNLLSVAYKNVVGRRSA  
WRVISSIEQKTDTSKKLQLIKDYREKVESELRSICTTVLELLDKYLIANATNPESKVFYLYK  
MKGDYFRYLAEVACGDDRKQTIDNSQGAYQEAFDISKKEMQPTHPIRLGLALNFSVFYY  
EILNPELACTLAKTAFDEAIAELDTLNEDSYKDSTLIMQLLRDNLTLWTSDSAGEECD  
AEGAEN

SEQ ID No:26

MDKNELVQKAKLAEQAERYDDMAACMKSVTEQGAELSNEERNLLSVAYKNVVGARRS  
SWRVVSSIEQKTEGAEEKKQQMAREYREKIE TELRDICNDVLSLLEKFLIPNASQAESKVF  
YLKMKGDYRYLAEVAAGDDKKGIVDQSQQAYQEAFEISKKEMQPTHPIRLGLALNFSV

FYYEILNSPEKACSLAKTAFDEAIAELDTLSEESYKDSTLIMQLLRDNLTWTSQTQGDEA  
EAGEGGEN

SEQ ID No:27

MGPASPAARGLSRRPGQPPLPLLLPLLLLLLRAQPAIGSLAGGSPGAPEAPGSAQVAGL  
CGRLTLHRDLRTGRWEPDPQRSRRCLRDPQRVLEYCRQMYPELQIARVEQATQAIPM  
ERWCGGSRSGSCAHPHHQVVPFRCLPGEFVSEALLVPEGCRFLHQERMDQCESSTR  
RHQEAQEACSSQGLILHGSGMMLPCGSDRFRGVEYVCCPPPGTPDPSGTAVGDPSTR  
SWPPGSRVEGAEDEEEEEESFPQPVDDYFVEPPQAEETVPPSSHTLAVVGKVTPT  
PRPTDGVDIYFGMPGEISEHEGFLRAKMDLEERRMRQINEVMREWAMADNQSKNLPK  
ADRQALNEHFQSILQTLEEQVSGERQRLVETHATRVIALINDQRRAALEGFLAALQADPP  
QAERVLLALRRYLRAEQKEQRHTLRHYQHVAAVDPEKAQQMRQVHHTLQVIEERVN  
QSLGLLDQNPFLAQELRPQIQELLHSEHLGPSELEAPAPGGSSSEDKGGLQPPDSKDDT  
PMTLPKGSTEQDAASPEKEKMNPLEQYERKVNASVPRGFPHSSEIQRDELAPAGTGV  
SREAVSGLLIMGAGGSLIVLSMLLLRRKKPYGAISHGVVEVDPMLTLEEQQRLRELQRH  
GYENPTYRFLEERP

SEQ ID No:28

MAATGTAAAAATGRLLLLLLVGLTAPALALAGYIEALAANAGTGFAVAEPQIAMFCGKLN  
MHVNIQTGKWEPDPTGTKSCFETKEEVLQYQCQEMYPELQITNVMEANQRVSIDNWCN  
RDKKQCKSRFVTPFKCLVGEFVSDVLLVPEKCQFFHKERMEVCENHQQHWHTVVKEAC  
LTQGMTLYSYGMMLPCGVDQFHGTEYVCCPQTKIIGSVSKEEEEEDEEEEEDEEED  
YDVYKSEFPTEADLEDFTEAAVDEDEDEDEEGEEVVEDRDYYYDTFKGDDYNEENPTE  
PGSDGTMSDKEITHDVKAVCSQEAMTGPCRAVMPRWYFDLSKGKCVRFIYGGCGGNR  
NNFESEDYCMVCKAMIPPTPLPTNDVDVYFETSADDNEHARFQKAKEQLEIRHRNRM  
DRVKKEWEEAELQAKNLPKAERQTLIQHFQAMVKALEKEAASEKQQLVETHLARVEAM  
LNDRRRMALENYLAALQSDPPRPHRILQALRRYVRAENKDRHLHTIRHYQHVLAVDPEKA  
AQMKSQVMTHLHVIEERRNQSLSLLYKVYPYVAQEIQEEIDELLQEQRADMDQFTASISE  
TPVDVRVSSEEESEEIPPFHPFHPFALPENEDTQPELYHPMKKSGSGVGEQDGGGLIGAE  
EKVINSKNKVDENMVIDETLDVKEMIFNAERVGGLLEERESVGPLREDFSLSSSSALIGLL  
VIAVAIATVIVISLVMLRKRQYGTISHGIVEVDPMLTPEERHLNKMQRNHGYENPTYKYLEQ  
MQI

SEQ ID No:29

MLPGLALLLLAAWTARALEVPTDGNAGLLAEPQIAMFCGRLNMHMNVQNGKWDS DPS  
 GTKTCIDTKEGILQYCQEVYPELQITNVVEANQPVTIQNWCKRGRKQCKTHPHFVIPYR  
 CLVGEFVSDALLVPDKCKFLHQERMDVCETHLHWHTVAKETCSEKSTNLHDYGMLLPC  
 GIDKFRGVEFVCCPLAEESDNVDSADAEEEDSDVWWGGADTDYADGSEDKVVEVAEE  
 EEVAEVEEEEADDDDEDEDGDEVEEEAEPEYEEATERTTSIATTTTTTTTESVEEVREV  
 CSEQAETGPCRAMISRWFYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMVCGSAMS  
 QSLLKTTQEPLARDPVKLPTTAASTPDAVDKYLET PGDENEHAHFQKAKERLEAKHRER  
 MSQVMREWEEAERQAKNLPKADKKAVIQHFQEKVESLEQEAANERQQLVETHMARVE  
 AMLNDRRRRLALENYITALQAVPPRPRHVFNMLKKYVRAEQKDRQHTLKHFEHVRMVDP  
 KKAQAIRSQVMTHLRVIYERMNQSLSLLYNVPAAVEEIQDEVDELLQKEQNYSDDLAN  
 MISEPRISYGNDALMPSLTETKTTVELLPVNGEFLDDLQPWHSFGADSV PANTENEVE  
 PVDARPAADRGLTTRPGSGLTNIKTEEISEVKMDAEFRHDSGYEVHHQKLVFFAEDVGS  
 NKGAIIGLMVGGVVIATVIVITLVMLKKKQYTSIHHGVVEVDAAVTPEERHLSKMQQNGY  
 ENPTYKFFEQM QN

SEQ ID No:30

MDAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIATVIVITLVMLKKKQYTSI  
 HHGVVEVDAAVTPEERHLSKMQQNGYENPTYKFFEQM QN

SEQ ID No:31

MALLAMHSWRWAAAAAAFEKRRHSAILIRPLVSVSGSGPQWRPHQLGALGTARAYQIP  
 ESLKSITWQRLGKGNSSGQFLDAAKALQVWPLIEKRTCWHGHAGGGLHTDPKEGLKDV  
 DTRKIIKAMLSYVWP KDRPD LRARVAISLGFLGGAKAMNIVVPMFKYAVDSL NQM SGN  
 MLNLS DAPNTVATMATAVLIGYGVS RAGAAFFNEVRNAVFGKVAQNSIRRIAKNVFLHL  
 HNLDLGFHLSRQTGALSKAIDRGTRGISFVLSALVFNLLPIMFEVMLVSGVLYYKCGAQF  
 ALVTLGTLGTYTAFTVAVTRWRTRFRIEMNKADNDAGNAAIDSLLNYETVKYFN NERYE  
 ACRYDGF LKTYETASLKSTSTLAMLNFGQSAIFSVGLTAIMVLASQGIVAGTLTVGDLVM  
 VNGLLFQLSLPLNFLGT VYRETRQALIDMNTLFTLLKVD TQIKDKVMASPLQITPQTATVA  
 FDNVHF EYIEGQKVLSGISFEVPAGKKVAIVGGSGSGKSTIVRLLFRFYEPQKGS IYLAG  
 QNIQDVSLES LRRAVGVVPQDAVLFHNTIYYNLLYGNISASPEEVYAVAKLAGLHDAILR  
 MPHGYDTQVGERGLKLSGGEKQRVAIARAILKDPPVILYDEATSSLD SITEETILGAMKD  
 VVKHRTSIFIAHRLSTVVD ADEIIVLDQGKVAERGTHHGLLANPHS IYSEMWH TQSSRVQ  
 NHDNPKWEAKKENISKEEERKKLQEEIVNSVKGCGNCSC

## SEQ ID No:32

MATVTATTKVPEIRDVTRIERIGAHSHIRGLGLDDALEPRQASQGMVGQLAARRAAGVV  
 LEMIREGKIAGRAVLIAGQP GTGKTAIAMGMAQALGPDPFTAAGSEIFSLEMSKTEALT  
 QAFRRSIGVRIKEETEIIIEGEVVEIQIDRPATGTGSKVGKLT LKTTMETIYDLG TKMIESL  
 TKDKVQAGDVITDKATGKISKLGSRFTRARDYDAMGSQTKFVQCPDGELQKRKEVVHT  
 VSLHEIDVINSRTQGFLALFSGDTGEIKSEVREQINAKVAEWREEGKAEIIPGVLFIDEVH  
 MLDIESFSFLNRALES DMAPVLIMATNRGITRIRGTSYQSPHGIPIDLLDRLLIVSTTPYSE  
 KDTKQILRIRCEEEDVEMSEDAYTVLTRIGLETSLRYAIQLITAASLVCRKRKGTEVQVDD  
 IKRVYSLFLDES RSTQYMKEYQDAFLF NELKGETMDTS

## SEQ ID No:33

MSVPSSLSQSAINANSHGGPALSLPLPLHAAHNQLLNAKLQATAVGPKDLRSAMGEGG  
 GPEPGPANAKWLKEGQNQLRRAATAHRDQNRNVTLT LAEEASQEP EMAPLGPKGLIHL  
 YSELELSAHNAANRGLRGPGLIISTQE QGPDEGEEKAAAGEAEEEEEDDDDEEEEEEDLS  
 SPPGLPEPLESVEAPPRPQALTDGPREHSKSASLLFGMRNSAASDEDSSWATLSQGSP  
 SYGSPEDTDSFWNPNAFETDSDLPAGWMRVQDTSGTYYWHIPTGTTQWEPPGRASP  
 SQGSSPQEESQLTWTGFAHGEGFEDGEFWKDEPSDEAPMELGLKEPEEGTLTFPAQS  
 LSPEPLPQEEELPPRNTNPGIKCFAVRSLGWVEMTEEELAPGRSSVAVNNCIRQLSYH  
 KNNLHDPMSGGWGEGKDLLLQLEDETLKLVEPQSQALLHAQPIISIRVWGVGRDSGRE  
 RDFAYVARDKLTQMLKCHVFRCEAPAKNIATSLHEICSKIMAERRNARCLVNGLSLDHS  
 KLVDVPFQVEFPAPKNELVQKFQVYYLGNVPVAKPVGVDVINGALESVLSSSSREQWT  
 PSHVSVAPATLTILHQQTEAVLGECRVRFLSFLAVGRDVHTFAFIMAAGPASFCCHMFW  
 CEPNAASLSEAVQAACMLRYQKCLDARSQASTSCLPAPPAESVARRVGWTVRRGVQS  
 LWGSLKPKRLGAHTP

## SEQ ID No:34

MQRRDDPAARMSRSSGRSGSMDPSGAHPSVRQTPSRQPPLPHRSRGGGGGSRGGA  
 RASPATQPPPLPPSATGPDATVGGPAPTLLPPSATASVKMEPENKYLPELMAEKDSL  
 DPSFTHAMQLLTAEIEKIQKGDSKKDDEENYDLDFSHKNMCLKERVLPVKQYPKFNFG  
 KILGPQGNTIKRLQEETGAKISVLGKGS MRD KAKEEELRKGGDPKYAHLNMDLHV FIEV  
 FGPPCEAYALMAHAMEEVKKFLVPDMMDDICQE QFLELSYLN GVPEPSRGRGV PVRG  
 RGAAPPPPPVPRGRGVGPPRGALVRGTPVRGAITRGATVTRGVPPPPTVRGAPAPRA  
 RTAGIQRIPLPPPAPETYEEYGYDDTYAEQSYEGYEGYYSQSQGDSEYYDYGHGEVQ  
 DSYEAYGQDDWNGTRPSLKAPPARPVKGAYREHPYGRY

SEQ ID No:35

MVKVTFNSALAQKEAKKDEPKSGEEALIIPDAVAVDCKDPDDVVPVGQRRRAWCWCM  
CFGLAFMLAGVILGGAYLYKYFALQPDDVYYCGIKYIKDDVILNEPSADAPAALYQTIEEN  
IKIFEEEEVEFISVPVPEFADSDPANIVHDFNKKLTAYLDLNLDKCYVIPLNTSIVMPPRNL  
LELLINIKAGTYLPQSYLIHEHMTDRIENIDHLGFFIYRLCHDKETYKLQRRETIKGIQKR  
EASNCFAIRHFENKFAVETLICS

SEQ ID No:36

MASRPRPRTPSRGPSDLRFRGEAGLRRVFLKKAGVRVRPADKRAAGSRVGCPWHRA  
EPPLGTREQQGFRKRERRWTGGRPGFAQAPPLGGPAQGALRQFPCDVAVGFTQEEW  
QHLDQAQRTPYRDMMLLENYSLLLSVGYCITKPEVVCKLEHGQVLWILEEESPSQSHLDC  
CIDDDLMEKRQENQDQHLQKVDFVNNKLTMDRNGVLGKTFSLDTNPILSRKIRGNCD  
SSGMNLLNNISELIISNRSSFVRNPAECNVRGKFLLCMKRENPYARGKPLEYDGNGKAVS  
QNEDLFRHQYIQTLLKQCFEYNQCGKAFHEEAACSTHKRVCSWETL

SEQ ID No:37

DVIVDINGNCVLGHTHADVVQMFQLVPVNQYVNLTLCRGYPLPDDSEDVVDIVAATPVI  
NGQSLTKGETCMNPQDFKPGAMVLEQNGKSGHTLTGDGLNGPSDASEQRVSMASG  
SSQPELVITIPLIKGPKGFGFAIADSPTGQKVKMILDSQWCQGLQKGDIIKEIYHQNVQNL  
HLQVVEVLKQFPVGADVPLILLRGGPPSPTKTAKMKTDKKENAGSLEAINEPIQPMPFP  
PSIIRSGSPKLPSEVYLKSKTLYEDKPPNTKDLDVFLRKQESGFGFRVLGGDGPDQSIY  
IGAIIPLGAAEKDGRRLRAADELMCIDGIPVKGKSHKQVLDLMTTAARNGHVLLTVRRKIFY  
GEKQPEDDSSQAFISTQNGSPRLNRAEVPARPAPEPYDVVLQRKENEGFGFVILTSK  
NKPPPGVIPHKIGRVIEGSPADRCGKLKVGDDHISAVNGQSIVELSHDNIVQLIKDAGVTVT  
LTVIAEEEEHHGPPSGTNSARQSPALQHRPMGQSQANHIPGDRSALEGEIGKDVSTSYR  
HSWSDHKHLAQPD TAVISVVGSRHNQNLGCYPVELERGPRGFGFSLRGGKEYNMGLF  
ILRLAEDGPAIKDGRIHVGDQIVEINGEPTQGITHTRAELIQAGGNKVLLLLRP GTGLIPD  
HGDWDINNPSSSNVIYDEQSPLPPSSHFA SIFEESHVPVIEESLRVQICEKAEELKDIVPE  
KKSTLNENQPEIKHQSL LQKNVSKRDPPSSHGHSNKKNLLKVENGVT RRRGRSVSPKKP  
ASQHSEEHLDKIPSPLKNNPKRRPRDQSLSPSKGENKSCQVSTRAGSGQDQCRKSRG  
RSASPKKQKQIEGSKAPSNAEAKLLEGKSRRRIAGYTGSNAEQIPDGKEKSDVIRKDAKQ  
NQLEKSRTSRPEKKIKRMVEKSLPSKMTNKTTSKEVSENEKGKKVTTGETSSSNDKIGE

NVQLSEKRLKQEPEEKVVS NKTEDHKGKELEAADKNKETGRFKPESSSPVKKTLITPGP  
WKVPSGNKVTGTIGMAEKRQ

SEQ ID No:38

MAGAGGGNDIQWCFSQVKGAVDDDVAEADIISTVEFNHSGELLATGDKGGRVVIFQQE  
QENKIQSHSRGEYNVYSTFQSHEPEFDYLSLEIEEKINKIRWLPQKNAAQFLLSTNDKTI  
KLWKISERDKRPEGYNLKEEDGRYRDPTTVTTLRVPVFRPMDLMVEASPRRIFANAHTY  
HINSISINSYETYLSADDLRINLWHLEITDRSFNIVDIKPANMEELTEVITAAEFHPNSCNT  
FVYSSSKGTIRLCDMRASALCDRHSKLFEEDPSNRSFFSEIISISDVKFSHSGRYMM  
TRDYLSVKIWDLN MENRPVETYQVHEYLRSKLCSLYENDCIFDKFECCWNGSDSVVMT  
GSYNNFFRMFDRNTKRDITLEASRENNKPRTVLKPRKVCASGKRKKDEISVDSLDFNKK  
ILHTAWHPKENIIAVATTNNLYIFQDKVN

SEQ ID No:39

MEKIRVCVRKRPLGMREVRERGEINIITVEDKETLLVHEKKEAVDLTQYILQHVIFYFDEVF  
GEACTNQDVYMKTTTHPLIQHIFNGGNATCFAYGQTGAGKTYTMIGTHENPGLYALAAK  
DIFRQLEVSQPRKHLFWWISFYEIYCGQLYDLLNRRKR LFAREDSKHMVQIVGLQELQV  
DSVELLLEVILKGSKERSTGATGVNADSSRSHAVIQIQKDSAKRTFGRISFIDLAGSERA  
ADARDSRQTKMEGAEINQSL LALKECIRALDQEHTHTPFRQSKLTQVLKDSFIGNAKT  
CMIANISPSHVATEHTLNTLRYADRVKELKKGICCTSVTSRNRTSGNSSPKRIQSSPGA  
LSEDKCSPKKVKLGFQQSLTVAAPGSTRGKVHPLTSHPPNIPFTSAPKVS GKRGGSRG  
SPSQEWVIHASPVKGTVRSGHVAKKKPEESAPLCSEKNRMGNKTVLGWESRASGPGE  
GLVRGKLSTKCKKVQTVQP VQKQLVSRVELSFGNAHHRAEYSQDSQRGTPARPASEA  
WTNIPPHQKEREHLRFYHQFQQPPLLQKQKLKYQPLKRS LRQYRPPEGQLTNETPPL  
FHSYSENHDGAQVEELDDSDFSDFS HISSQRATKQRNTLENSEDSFFLHQTWGQG  
PEKQVAERQQSLFSSPRTGDKKDLTKSWVDSRDPINHRRALDHSCSPSKGPVDWSR  
ENSTSSGSPRDSLAEKPYCSQVDFIYRQERGGGSSFDLRKDASQSEVSGENEGNLP  
SPEEDGFTISLSHVAVPGSPDQRDTVTTPLREVSADGPIQVTSTVKNGHAVPGEDPRG  
QLGTHAEYASGLMSPLTMSLLENPDNEGSP PSEQLVQDGATHSLVAESTGGPVVSHTV  
PSGDQEAALPVSSATRHLWLSSSPDNKPGGDLPALSPSPIRQH PADKLPSREADLGE  
ACQSRETVLFSHEHMGSEQYDADAEETGLDGSWGFGPKPFTTIHMGVPHSGPTLTPR  
TGSSDVADQLWAQERKHPTRLGWQEFGLSTDPIKLPCNSENVTWLKPRPISRCLARPS  
SPLVPSCSPKTAGTLRQPTLEQAQQVVIRAHQEQLDEMAELGFKEETLMSQLASNDFE  
DFVTQLDEIMVLKSKCIQSLRSQLQLYLTCHGPTAAPEGTVPS

SEQ ID No:40

MATSEQSICQARASVMVYDDTSKKWVPIKPGQQGFSRINIYHNTASNTFRVVGVLQD  
 QQVVINYSIVKGLKYNQATPTFHQWRDARQVYGLNFASKEEATTFSNAMLFALNIMNSQ  
 EGGPSSQRQVQNGPSPDEMDIQRQVMEQHQQQRQESLERRTSATGPILPPGHPSS  
 AASAPVSCSGPPPPPPPPVPPPTGATPPPPPLPAGGAQGSSHDESSMSGLAAGAAIAG  
 AKLRRVQRPEDASGGSSPSGTSKSDANRASSGGGGGGLMEEMNKLLAKRRKAASQS  
 DKPAEKKEDESQMEDPSTSPSPGTRAASQPPNSSEAGRKPWERSNSVEKPVSSILSRT  
 PSVAKSPEAKSPLQSQPHSRMKPAGSVNDMALDAFDLDRMKQEILEEVVRELHKVKEE  
 IIDAIRQELSGISTT

SEQ ID No:41

MDFQHRPGGKTGSGGVASSSESNRDRRERLRQLALETIDINKDPYFMKNHLGSECKL  
 CLTLHNNESYLAHTQGKKHQTNLARRAAKEAKEAPAQPAPEKVKEVEKKFVKIGRPG  
 YKVTQQRDSEMGGQSLLFQIDYPEIAEGIMPRHRFMSAYEQRIEPPDRRWQYLLMAAE  
 PYETIAFKVPSREIDKAEGKFWTHWNRETQFFLQFHFKMEKPPAPPSLPAGPPGVKR  
 PPPPLMNGLPPRPPLPESLPPPPPGGLPLPPMPPTGPAPSGPPGPPQLPPPAPGVHPP  
 APVVHPPASGVHPPAPGVHPPAPGVHPPAPGVHPPPTSGVHPPAPGVHPPAPGVHPPA  
 PGVHPPAPGVHPPAPGVHPPPSAGVHPQAPGVHPPAAPAVHPQAPGVHPPAPGMHPQ  
 APGVHPQPPGVHPSAPGVHPQPPGVHPSNPGVHPPTMPPPMLRPPLPSEGPNIPPP  
 PPTN

SEQ ID No:42

MAWALKLPLADEVIESGLVQDFDASLSGIGQELGAGAYSMSDVLALPIFKQEESLPPD  
 NENKILPFQYVLCAATSPAVKLHDETLYLNQGGQSYEIRMLDNRKLGELPEINGKLVKSIF  
 RVVFHDRRLQYTEHQQLEGWRWNRPGDRILDIDIPMSVGIIDPRANPTQLNTVEFLWDP  
 AKRTSVFIQVHCISTEFTMRKHGGEKGVPPFRVQIDTFKENENGEYTEHLHSASCQIKVFK  
 PKGADRKQKTDREKMEK RTPHEKEKYQPSYETTILTECSPWPEITYVNNSPSPGFNSS  
 HSSFSLGEGNGSPNHQPEPPPPVTDNLLPTTTPQEAQQWLHRNRFSTFTRLFTNFSGA  
 DLLKLTRDDVIQICGPADGIRLFNALKGRMVRPRLTIYVCQESLQLREQQQQQQQQQK  
 HEDGDSNGTFFVYHAIYLEELTAVELTEKIAQLFSISPCQISQIYKQGPTGIHVLISDEMIQ  
 NFQEEACFILDTMKAETNDSYHIILK

SEQ ID No:43

MQEDRDGSCSTVGGVGYGDSKDCILEPLSLPESPGGTTTLEGSPSVPCIFCEEHFPVA  
 EQDKLLKHMIIIEHKIVIADV KLVADFQRYILYWRKRFT EQPITDFCSVIRINSTAPFEEQEN  
 YFLLCDVLPEDRILREELQKQRLREILEQQQQERNDTNFHGVCMFCNEEFLGNRSVILN  
 HMAREHAFNIGLPDNIVNCNEFLCTLQKKLDNLQCLYCEKTFRDKNTLKD HMRKKQHR  
 KINPKNREYDRFYVINYLELGKSWE EVQLEDDRELLDHQEDDWSDWEEHPASAVCLFC  
 EKQAETIEKLYVHMEDAHEFDLLKIKSELGLNFYQQVKLVNFIR RQVHQCR CYGCHVKF  
 KSKADLRTHMEETKHTSLLPDRKTWDQLEYFPTYENDTLLCTLSDSESDLTAEQNE  
 NVPISEDTSKLYALKQSSILNQLLL

SEQ ID No:44

MRLTHICCCLLYQLGFLSNGIVSELQFAPDREEWEVVPALWRREPVDPA GSGGSA  
 DPGWVRGVGGGGSARAQAAGSSREVR SVAPVPLEEPVEGRSESRLRPPPPSEGEED  
 EELESQELPRGSSGAAALSPGAPASWQPPPPQPPPSPPPAQHAEPDGDDEVLLRIPAF  
 SRDLYLLLRRDGRFLAPRFAVEQRPNPGPGPTGAASAPQPPAPPDAGCFYTGA VLRHP  
 GSLASFSTCGGGLMGFIQLNEDFIEPLNDTMAITGHPHRVYRQKRSMEEKVTEKSAL  
 HSHYCGIISDKGRPRSRKIAESGRGKRYSYKLPQEYNIETVVADPAMVSYHGADAARR  
 FILTILNMVFNLFQHKS LGVQVNL RVIKLILLHETPPELYIGHHGEKMLESFCKWQHEEFG  
 KKNDIHLEMSTNWGEDMTSVDAAILTRKDFCVHKDEPCDTVGIAYLSGMCSEKRK CIIA  
 EDNGLNL AFTIAHEM GHNMGINHDNDHPSCADGLHIMSGEWIKGQNLGDVSWSRCSK  
 EDLERFLRSKASNCLLQTNPQSVNSVMVPSKLPGMTYTADEQCQILFGPLASFCQEMQ  
 HVICTGLWCKVEGEKECRTKLDPPMDGTDCDLGKWCKAGECTSRTSAPEHLAGEWSL  
 WSPCSRTCSAGISSRERKCPGLDSEARDCNGPRKQYRICENPPCPAGLPGFRDWQCQ  
 AYSVRTSSPKHILQWQAVLDEEKPCALFCSPVGKEQPILLSEKVM DGTSCGYQGLDICA  
 NGRCQKVGCDGLLGSLAREDHCGVCNGNGKSKKIIKGDFNHTRGAGYVEVLVIPAGAR  
 RIKVVEEKPAHSYLALRDAGKQSINSDWKIEHSGAFNLAGTTVHYVRRGLWEKISAKGP  
 TTAPLHLLVLLFQDQNYGLHYEYTIPSDPLPENQSSKAPEPLFMWTHTSWEDCDATCG  
 GGERKTTVSCTKIMSKNISIVDNEKCKYLTKPEPQIRKCNEQPCQTRWMMTEWTPCSR  
 TCGKGMQSRQVACTQQLSNGTLIRARERDCIGPKPASAQRC EGQDCMTVWEAGVWS  
 EFSVKCGKGIRHRTVRCTNPRKKCVLSTRPREAEDCEDYSKCYVWRMGDWSKCSITC  
 GKGMQSRVIQCMHKITGRHGNECFSSSEKPAAYRPCHLQPCNEKINVNTITSPRLAALTF  
 KCLGDQWPVYCRVIREKNLCQDMRWYQRCCETCRDFYAQKLQQKS

SEQ ID No:45

MMKLYIDNAAPDKLKGLCFFVRCRNDVAINVKTIQEEALFTVLDASKGLLNGIRDMLANI  
 FLPAVLATNNWGALNQSKQGESEKHIFTETINRYLSFLDGARISIEGTVKLKTIDNVNFSK  
 LHTFEEVTAASNSSETVHQLEEVLMVWYKQIEQVLIIESEQMRKEAGDSGPLTELEHWK  
 RMSAKFNIIIEQIKGPSCKAVINVLNVAHSLKLLKNWRDLARITDTANESKDNVRYLYTLE  
 KVCQPLYNHDLVSMAGIQNLINAIIRMIHGVSRYNTSERMTSLFIKVTNQMV TACKAYI  
 TDGGLNHVWDQETPVVLKKIQDCIFLFKEYQASFHKTRKLISESSGEKSFEVSEMYIFGK  
 FEAFCRLEKITEMITVVQTYSTLSNSTIEGIDIMAIKFRNIYQGVKKKQYDILDPRRTEFD  
 TDFLDFMTKINGLEVQIQAFMNSSFGKILSSQQALQLLQRFQKLNIPCLGLEINH TIERILQ  
 YYVAELDATKKASLYHSQKDDPPLARNMPPIAGKILWVRQLYRRISEPINYFFKNSDILSS  
 PDGKAVIRQYNKISYVLVEFEVYHTAWIREISQLHYALQATLFRHPETGKLLVNFDPKI  
 LEVVRETCKMIKMKLDVPEQAKRLLKLESKLKADKLYLQGLLQYYDEL CQEVP SVFVNL  
 MTPKMKKVESVLRQGLTVLTWSSLTLESFFQEVELVLD MFNQLLKKISDLCEMHIDTVLK  
 EIAKTVLISLPESGATKVEDMLTLNETYTKEWADILNHKSKHVEEAVRELISIFEQIYEVKY  
 TGKVQKQSEQRKHVVFVGSETGEGENNDYEANIVNEFDTHDKEDEFKKECKEVFAFFSH  
 QLLDSLQKATRLSLDTMKRRIFVARQVENMLIILYGRKQSEDIISFIKSEVHLAIPNVVMIP  
 SLDDIQQAINRMIQLTLEVSRGVAHWGQQQIRPIKSVIPSPTTTDVTHQNTGKLLKKEER  
 SFEEAIPARKLKNFYPGVAEHKDISKLVLSSSVNSLRKAAHEALQDFQKYKTLWTEDR  
 DVKVKEFLANNPSLTEIRSEILHYATFEQEIDELKPIIVVGALELHTEPMKLALSIEAKAWK  
 MLLCRYLNEEYKKKMSYMI AFINEYLKKLSRPIRDLDVRFAMEALSCIRDNEIQMDMTL  
 GPIEEAYAILNRFEVEVTKEESEAVDTLRYSFNKLQSKAVSVQEDLVQVQPKFKSNLLES  
 VEVFREDVINFAEAYELEGPMPVNIPPQEASNRLQIFQASFDDLWRKFVTYSSGEQLFG  
 LPVTDYEVVHKTRKELNLLQKLYGLYDTVMSSISGYEILWGDVDIEKINAEELLE FQNRC  
 RKLPGKGLKDWQAFLDLKKRIDDFSESCPLLEMMTNKAMKQRHWDRISELTGTPFDVES  
 DSFCLRNIMEAPLLKHKDDIEDICISAIKEKDIEAKLTQVIENWTNQNL SFAAFKKGK GELL  
 KGTESGEIITLMEDSLMVLGSLLSNRYNAPFKKNIQNWVYKLSTSSDIIEEWLVVQNLWV  
 YLEAVFVGGDIAKQLPQEAKRFQNIKSWIKIMQRAHENPNVINCCVGD ETMGQLLPHL  
 HEQLEVCQKSLTGYLEKKRLLFPRFFVSDPVILLEILGQASDSHTIQPHLPAVSDNINEVT  
 FHAKDYDRIMAVISREGEKIVLDNSVMAKGPVEIWLLDLLKMQMSSLHNIIRSAFYQISDS  
 GFQLLPFLSHFPAQVGLLGIQMLWTHDSEEALRNAKDDR KIMQVTNQKFLDILNTLISQT  
 THDLSKFDRVKFETLITIHVHQRDIFDDLVKMHIKSPTDFEWLQSRFYFKEDLDQTVVSI  
 TDVDFIYQNEFLGCTDRLVITPLTDRCYITLAQALGMNMGGAPAGPAGTGKTETTKDMG  
 RCLGKYVVVFNCSQMDFRGLGRIFKGKCLAQSGSWGCFDEFNRIELPVLSVAAQQIYI  
 VLTARKERKKQFIFSDGDCVDLNPEFGIFLTMPGYAGRQELPENKIQFRTVAMMVPDR  
 QIIMRVKLASCGFLENVILAQKFYVLYKLCEEQLTKQVHYDFGLRNILSVLRTLGSQKRAR

PEDSELSIVMRGLRDMNLSKLVDEDEPLFSLINDLFPGLQLDSNTYAELQNAVAHQVQI  
 EGLINHPPWNLKLVQLYETSLVRHGLMTLGPSSGSGKTTVITLMKAQTECGRPHREMRM  
 NPKAITAPQMFGRLDTATNDWTDGIFSTLWRKTLKAKKGENIFLILDGPVDAIWENLNSV  
 LDDNKTTLTANGDRIPMAPSCKLLFEVHNIEENASPATVSRMGMVYISSSALSWRPILQA  
 WLKKRTAQEA AVFLTYEKVFEDTYTYMKLNLNPKMQLLECNYIVQSLNLEGLIPSKEE  
 GGVSCVEHLHKL FVFGLMWSLGALLELESREKLEAFLRQHESKLDLPEIPKGSNQTMYE  
 FYVTDYGDWEHWNKKLQPYYP TDSIPEYSSILVPNVNIRTNFLIDTIAKQHKAVLLTG  
 EQGTAKTMVKAYLK KYDPEVQLSKSLNFSSATEPMMFQRTIESYVDKRIGSTYGPPG  
 GRKMTVFIDDINMPVINEWGDQITNEIVRQMMEMEGMYSLDKPGDFTTIVDVQLIAAMIH  
 PGGGRNDIPQRLKRQFTVFNCTLPSNASIDKIFGIIGCGYFDCRSFKPQICEMIVNLVSV  
 GRVLWQWTKVKMLPTPSKFHYIFNL RDLSRIWQGM LTIKAEECASIPTLLSLFKHECSR  
 IADR FITPEDEQWFNAHLTRAVEENIGSDAASCILPEPYFVD FLREMPEPTGDEPEDSVF  
 EVPKIYELMP SFDFLA EKLQFYQRQFNEIIRGTSLDLVFFKDAMTHLIKISRIIRTSCGNALL  
 VGVGGSGKQSL SRLASFIAGYQIFQITLRSYNVTNL TDDLKALYKVAGADGKGITFIFTD  
 SEIKDEAFLEYLNNLLSSGEISNLFARDEMDEITQGLISVMKRELPRHPPTFDNLYEYFIS  
 RSRKNLHVVL CFSPVGEKFRARSLKFPGLISGCTMDWFSRWPREALIAVASYFLSDYNI  
 VCSSEIKRQVVETMGLFHDMVSESCESYFQRYRRRAHVTPKSYLSFINGYKNIYAEKVK  
 FINEQAERMNIGLDKLMEASESVAKLSQDLAVKEKELAVASIKADEVLA EVTVSAQASAK  
 IKNEVQEVKDKAQKIVDEIDSEKVKAESKLEAAKPALEEAEEAALNTIKPNDIATVRKLAKP  
 PHLIMRIMDCVLLL FQKKIDPVTMDPEKSCCKPSWGESLKLMSATGFLWSLQQFPKDTI  
 NEETVELLQPYFNMD DYT FESAKKVCGNVAGLLSWTLAMAIFYGINREVLPLKANLAKQ  
 EGR LAVANAELGKAQALLDEKQAELDKVQAKFDAAMNEKMDLLNDADTCRKKMQAAS  
 TLIDGLSGEKIRWTQQSKEFKAQINRLVGDILLCTGFLSYLGPFNQIFRNYLLKDQWEME  
 LRARKIPFTENLNLISMLVDPPTIGEWGLQGLPGDDLSIQNGIIVTKATRYPLIDPQTQGK  
 TWIKSKEKENDLQVTSLNH KYFRTHLED SLSLGRPLIEDIHEELDPALDNVLEKNFIKSG  
 TTFKVKGDK ECDIMDTFKLYITTKLPNPAFTPEINAKTSVIDFTVTMKGLENQLLRRVILT  
 EKQELEAERVKLL EDVTFNKRKMKELEDNLLYKLSATKGS LVDDESLIGVLRRTTKQTAAE  
 VSEKLHVAAETEIKINAAQEEFRPAATRG SILEYFLITEMSMVNIMYQTS LAQFLKLF DQSM  
 ARSEKSP LPQKRITNII EYLT YEVTYSVRGLYENHKFLFVLLMTLKIDLQRGTVKHREFQ  
 ALIKGGAALDLKACPPKPYRWILD MTWNLVELSKLPQFAEIMNQISRNEKGWKS WFDK  
 DAPEEEIIPDGYNDSLDTCHKLLLIRSWCPDRTVFQARKYIADSLEEKYTEPVILNLEKTW  
 EESDTRTPLICFLSMGSDPTNQIDALAKKLEKRTISMGGQGEVHARKLIQMSMQGGG  
 WVLLQNCHLGLFMEELLETLITTEASDD SFRVWITTEPHDRFPITLLQTS LKFTNEPPQ  
 GVRAGLKRTFAGINQDLLDISNLP MWKPM LYTVAFLHSTVQERRKFGPLGWNIPYEFNS

ADFSASVQFIQNHLECDIKKGVSWNTVRYMIGEVQYGGRVTDDFDKRLLNCFARVWF  
 SEKMFEPSCFYTYGYKIPLCKTLDQYFEYIQSLPSLDNPEVFGLHPNADITYQSNTASAV  
 LETITNIQPKESGGGVGETREAIYRLSEDMLSKLPPDYIPHEVKSRLIKMGHLNSMNIFL  
 RQEIDRMQRVISILRSSLDLKLAIEGTIIMSENLRDALDNMYDARIPQLWKRVSWDSSTL  
 GFWFTELLERNAQFSTWIFEGRPNVFWMTGFFNPQGFLTAMRQEVTRAHKGWALDTV  
 TIHNEVLRQTKEEITSPPGEGVYIYGLYMDGAAWDRRNGKLMESTPKVLFTQLPVLHIFA  
 INSTAPKDPKLYVCPIYKKPRRTDLTFITVVYLRTVLSPDHWILRGVALLCDIK

SEQ ID No:46

MRSPATGVPLPTPPPPLLLLLLLLLLPPPLLGDQVGPCRSLSRGRGSSGACAPMGWLC  
 PSSASNLWLYTSRCRDAGTELTGHLVPHHDGLRVWCPESEAHIPPPAPEGCPWSCR  
 LLGIGGHLSPQGKLTLP EEHPCLKAPRLRCQSCKLAQAPGLRAGERSPEESLGGRKR  
 NVNTAPQFQPPSYQATVPENQPAGTPVASLRAIDPDEGEAGRLEYTMDALFDSRSNQF  
 FSLDPVTGAVTTAEELDRETKSTHVFRVTAQDHGMPRRSALATLTILVTDTNDHDPVFE  
 QQEYKESLRENLEVGYEVLTVRATDGDAPPNANILYRLLLEGSGGSPSEVF EIDPRSGVI  
 RTRGPVDREEVESYQLTVEASDQGRDPGRSTTA AVFLSVEDDNDNAPQFSEKRYV  
 QVREDVTPGAPVLRVTASDRDKGSNAV VHYSIMSGNARGQFYLDAQTGALDVVSPLDY  
 ETTKEYTLRVRAQDGGRPPLSNVSGLTVQVLDINDNAPIFVSTPFQATVLESVPLGYLV  
 LHVQAIDADAGDNARLEYRLAGVGHDFFPTINNGTGWISVAAELDREEVD FYSFGVEAR  
 DHGTPALTASASVSVTVLDVNDNNPTFTQPEYTVRLNEDAAVGTSVTVSAVDRDAHS  
 VITYQITSGNTRNRFSITSQSGGGLVSLALPLDYKLERQYVLAVTASDGTRQDTAQIVVN  
 VTDANTHRPVFQSSH YTVNVNEDRPAGTTVVLISATDEDTGENARITYFMEDSIPQFRID  
 ADTGAVTTQAE LDYEDQVSYTLAITARDNGIPQKSDTTYLEILVNDVNDNAPQFLRDSYQ  
 GSVYEDVPPFTSVLQISATDRDSGLNGRVFYTFQGGDDGDGDFIVESTSGIVRTLRRLD  
 RENVAQYVLRAYAVDKGMPPPARTPMEVTVTVLDVNDNPPVFEQDEFDVFVEENSPIGL  
 AVARVTATDPDEGTNAQIMYQIVEGNIPEVFQLDIFSGELTALVDLDYEDRPEYVLVIQAT  
 SAPLVSRATVHVRLLDRNDNPPVLGNFEILFN NYVTNRSSSFPGGAIGRVPAHDPDISD  
 SLTYSFERGNELSLVLLNASTGELKLSRALDNNRPLEAIMSVLVSDGVH SVTAQCALRVT  
 IITDEMLTHSITLRLEDMSPERFLSPLLGLFIQAVAA TLATPPDHVVVFNVQRDTDAPGGH  
 ILNVSLSVGQPPPGPGGGPPFLPSED LQERLYLNRSLLTAISAQRVLPFDDNICLREPCEN  
 YMRCVSVLRFDSSAPFIASSSVLFRPIHPVGGLRCRCPPGFTGDYCETEVDLCYSRPCG  
 PHGRCRSREGGYTCLCRDGYTGEHCEVSARSGRCTPGVCKNGGTCVNLLVG GFKCD  
 CPSGDFEKP YCQVTTRSFP AHSFITFRGLRQRFHFTLALS FATKERDGLLLYNGRFNEK  
 HDFVALEVIQE QVQLTFSAGESTTTVSPFVPGGVSDGQWHTVQLKYYNKPLL GQTGLP

QGPSEQKVAVVTVDGCDTGVALRFGSVLGNYSCAAQGTQGGSKKSLDLTGPLLLGGV  
 PDLPEFVVRMRQFVGCMRNLQVDSRHIDMADFIANNGTVPGCPAKKNVCDSNTCHN  
 GGTCVNQWDAFSCCEPLGFGGKSCAQEMANPQHFLGSSLVAWHGLSLPISQPWYLSL  
 MFRTRQADGVLLQAITRGRSTITLQLREGHVMLSVEGTGLQASSLRLEPGRANDGDWH  
 HAQLALGASGGPGHAILSFDYGQQRAEGNLGPRLHGLHLSNITVGGIPGPAGGVARGF  
 RGCLQGVRVSDTPEGVNSLDPSHGESINVEQGCSLPDPCDSNPCPANSYCSNDWDSY  
 SCSCDPGYYGDNCTNVCDLNPCEHQSVCTRKPSAPHGYTCECPPNYLGPYCETRIDQ  
 PCPRGWWGHPTCGPCNCDVSKGFDPDCNKTSGECHCKENHYRPPGSPCTCLLCDYCYP  
 TGSLSRVCDPEDGQCPCPKPGVIGRQCDCRCDNPFAEVTNGCEVNYDSCPRAIEAGIW  
 WPRTRFGLPAAAPCPKGSFGTAVRHCDHRGWLPNLFNCTSFSEKKGFAERLQRN  
 ESGLDSEGRSQQLALLLRNATQHTAGYFGSDVKVAYQLATRLLAHESTQRGFGLSATQD  
 VHFTENLLRVGSALLDTANKRHWELIQQTEGGTAWLLQHYEAYASALAQNMRYTYLSP  
 FTIVTPNIVISVVRDLKGNFAGAKLPRYEALRGEQPPDLETTVILPESVFRETTPVVRPAG  
 PGEAQEPEELARRQRRHPELSQGEAVASVYIYRTLAGLLPHNYDPDKRSLRVPKRPIINT  
 PVVSISVHDDEELLPRALDKPVTVQFRLLETEERTKPICVFWNHSILVSGTGGWSARGC  
 EVVFRNESHVSCQCNHMTSFAVLMDVSRRENGEILPLKTLTYVALGVTLAALLLTFFFLT  
 LLRILRSNQHGIRRNLTAAALGLAQLVFLGINQADLPFACTVIAILLHFLYLCTFSWALLEAL  
 HLYRALTEVRDVNTGPMRFYYMLGWGVPAFITGLAVGLDPEGYGNPDFCWLSIYDTLI  
 WSFAGPVAFVAVSMSVFLYILAAARASCAAQRQGFEEKGPVSGLQPSFAVLLLLSATWLLA  
 LLSVNSDTLLFHLYFATCNCIQGPFIFLSYVVLKEVRKALKLACSRKPSDPALTTKSTL  
 TSSYNCPSPYADGRLYQPYGDSAGSLHSTSRSGKSQPSYIPFLLREESALNPGQGPPG  
 LGDPGSLFLEGQDQHDPTDSDSDLSLEDDQSGSYASTHSSDSEEEEEEEEEEEAAAF  
 PGEQGWDSLLGPGAERLPLHSTPKDGGPGPGKAPWPGDFGTAKESSGNGAPEERL  
 RENGDALSREGSLGPLPGSSAQPHKILKKKCLPTISEKSSLLRPLEQCTGSSRGSSA  
 SEGSRGGPPPRPPPRQSLQEQLNGVMPIAMSIKAGTVDEDSSGSEFLFFNFLH

SEQ ID No:47

MLRRPAPALAPAARLLLAGLLCGGGVWAARVNKHKWPWLEPTYHGIVTENDNTVLLDPP  
 LIALDKDAPLRFAESFEVTVTKEGEICGFKIHGQNVFPDAVVVDKSTGEGVIRSKEKLDC  
 ELQKDYSFTIQAYDCGKGPDTGNVKKSHKATVHIQVNDVNEYAPVFKEKSYKATVIEGK  
 QYDSILRVEAVDADCSPQFSQICSYEITPDVPFTVDKDGKNTTEKLNKGKEHQYKLTVT  
 AYDCGKKRATEDVLVKISIKPTCTPGWQGWNNRIEYEPGTGALAVFPNIHLETCDPEVA  
 SVQATVELETSHIGKGCDDTYSEKSLHRLCGAAAGTAELLSPSPSGSLNWTMGLPTDN  
 GHDSQVFEFNGTQAVRIPDGVVSVSPKEPFTISVWMRHGPFGRKKETILCSSDKTDM

NRHHYSLYVHGCRLIFLFRQDPSEEKKYRPAEFHWKLNQVCDEEWHHYVLNVEFPSVT  
 LYVDGTSHEPFSVTEDYPLHPSKIETQLVVGACWQEFSGVENDNETEPVTVASAGGDL  
 HMTQFFRGNLAGLTLRSGKLADKKVIDCLYTCKEGLDLQVLEDSGRGVQIQAHPSQLVL  
 TLEGEDLGELDKAMQHISYLSNRQFPTPGIRRLKITSTIKCFNEATCISVPPVDGYVMVLQ  
 PEEPKISLSGVHHFARAASEFESSEGVFLFPELRIISTITREVEPEGDGAEDPTVQESLVS  
 EEIVHDLDTC EVTVEGEELNHEQESLEVDMARLQQKGIEVSSSELGMTFTGVDTMASY  
 EEVLHLLRYRNWHARSLLDRKFKLICSELNGRYISNEFKVEVNVIIHTANPMEHANHMAA  
 QPQFVHPEHRSFVDLSGHNLANPHFPAVVPSTATVVIVVCVSFLVFMILGVFRIRAAHR  
 RTMRDQDTGKENEMDWDDSAITITVNPMETYEDQHSSEEEEEEEEEEESEEDGEEDD  
 ITSAESESSEEEEEGEQGDQPQATRRQQLEWDDSTLSY

SEQ ID No:48

MLPGRLCWVPLLLALGVGSGSGGGGDSRQRRLLAAKVNKHKPWIIETSYHGVITENNDT  
 VILDPPLVALDKDAPVPFAGEICAFKIHGQELPF EAVVLNKTSGEGRRLRAKSPIDCELQKE  
 YTFIIQAYDCGAGPHETA WKKSHKAVVHIQVKDVNEFAPTFKEPAYKAVVTEGKIYDSIL  
 QVEAIDEDCSPQYSQICNYEIVTTDVPFAIDRNGNIRNTEKLSYDKQHQQYEILVTAYDCG  
 QKPAAQDTLVQVDVKPVCKPGWQDWT KRIEYQPGSGSMPLFPSIHLETCDGAVSSLQI  
 VTELQTNIGKGC DRETYSEKSLQKLCGASSGIIDLLPSPSAATNWTAGLLVDSSEMIFK  
 FDGRQGAKIPDGIVPKNLTDQFTITMWMKHGSPSPGVRAEKETILCNSDKTEMNRHHYAL  
 YVHNCRLVFLLRKDFDQADTFRPAEFHWKLDQICDKEWHYYVINVEFPVVTLYMDGAT  
 YEPYLVTDNWPIHP SHIAMQLTVGACWQGGEVTKPQFAQFFHGS LASLTIRPGKMESQ  
 KVISC LQACKEGLDINSLES LGQGIKYHFNPSQSILVMEGDDIGNINRALQKVSYINSRQF  
 PTAGVRR LKVSSKVQCFGEDVCISIPEVDAYVMVLQAIEPRITLRGTDHFWRPAAQFES  
 ARGVTLFPDIKIVSTFAKTEAPGDVKTTDPKSEVLEEMLHNLD FCDILVIGGDLDPRQECL  
 ELNHSELHQRHLDATNSTAGYSIYGVGSM SRYEQVLHHIRYRNWRPASLEARRFRIKC  
 SELNGRYTSNEFNLEVSILHEDQVSDKEHVNHLIVQPPFLQSVHHPESRSSIQHSSVVP  
 SIATVVIISVCMLVFV VAMGVYRVRIAHQHFIQETEA AKESEMDWDDSAITITVNPMEKH  
 EGP GHGEDETEGEEEEEEAEEEMSSSSSGSDDSEEEEEEEGMGRGRHGGQNGARQAQL  
 EWDDSTLPY

SEQ ID No:49

MTLLLLPLLLASLLASCSCNKANKHKPWIEAEYQGIVMENDNTVLLNPPLFALDKDAPLR  
 YAGEICGFR LHGSGVPFEAVILDKATGEGLIRAKEPVDCEAQKEHTFTIQAYDCGEGPD  
 GANTKKSHKATVHVRVNDVNEFAPVFVERLYRAAVTEGKLYDRILRVEAIDGDCSPQYS

QICYEILTPNTPFLIDNDGNIENTEKLQYSGERLYKFTVTAYDCGKKRAADDAEVEIQVK  
PTCKPSWQQGWNKRIEYAPGAGSLALFPGIRLETCDLWNIQATIELQTSHVAKGCDRD  
NYSERALKLGAATGEVDLLPMPGPANWNTAGLSVHYSQDSSLIYWFNGTQAVQVP  
LGGPSGLGSGPQDLSLSDHFTLSFWMKHGVTNPKGKKEETIVCNTVQNEDEGFSHYSLT  
VHGCRIAFLYWPLLESARPVKFLWKLEQVCDDEWHHYALNLEFPTVTLTYTDGISFDPALI  
HDNGLIHPPRREPALMIGACWTEENKEKEKGDNSTDTTQGDPLSIHHYFHGYLAGFS  
VRSGRLESREVIECLYACREGLDYRDFESLGKGMKVHVNPSQSLLTLEGDDVETFNHA  
LQHVAYMNTLRFATPGVRPLRLTTAVKCFSEESCVSIPVEGYVVVLQPDAPQILLSGTA  
HFARPAVD FEGTNGVPLFPDLQITCSISHQVEAKKDESWQGTVDTRMSDEIVHNLG  
CEISLVGDDLDPERESLLDTSLSLQQRGLELTNTSAYLTIAGVESITVYEEILRQARYRLR  
HGAALYTRKFRSLSCSEMNGRYSSNEFIVEVNVLHSMNRVAHPSHVLSSQQFLHRGHQP  
PPEMAGHSLASSHRNSMIPSAATLIIVCVGFLVLMVVLGLVRIHSLHRRVSGAGGPPGA  
SSDPKDPDLFWDDSAITIVNPMESYQNRQSCVTGAVGGQGEDEDSSDSEVADSPSS  
DERRIETPPHRY

SEQ ID No:50

MYIKQVIIQGFRSYRDQTIVDPFSSKHNVIVGRNGSGKSNFFYAIQFVLSDEFSHLRPEQ  
RLALLHEGTGPRVISAFVEIIFDNSDNRLPIDKEEVSLRRVIGAKKDQYFLDKKMTKNDV  
MNLLESAGFSRNPYYIVKQGKINQMATA PD SQRLKLLREVAGTRVYDERKEESISLMK  
ETEGKREKINELLKYIEERLHTLEEEKEELA QYQKWDKMRRALEYTIYNQELNETRAKLD  
ELSAKRETSGEKSRQLRDAQQDARDK MEDIERQVRELKTKISAMKEEKEQLSAERQEQ  
IKQRTKLELKAKDLQDEL AGNSEQRKRLKERQKLEKIEEKQKELAETEPKFNSVKEKE  
ERGIARLAQATQERTDLYAKQGRGSQFTSKEERDKWIKKELKSLDQAINDKKRQIAAIHK  
DLEDTEANKEKNLEQYNKLDQDLNEVKARVEELDRKYEVKNKKDELQSERNYLWREE  
NAEQQALAAKREDLEKKQQLLRAATGKAILNGIDSINKVLDHFRRKGINQHVGNGYHGIV  
MNNFECEPAFYTCVEVTAGNRLFYHIVDSDEVSTKILMEFNKMNLPGEVTFPLPNKLDV  
RDTAYPETNDAIPMISKLRYNPRFDKAFKHVFGKTLICRSMEVSTQLARAFTMDCITLEG  
DQVSHRGALTGGYYDTRKSRLELQKDVRKAEELGELEAKLNENLRNRIERINNEIDQL  
MNQMQQIETQQRKFKASRDSILSEM KMLKEKRQQSEKTFMPKQRSLSLEASLHAME  
STRESLKAELGTDLLSLSLEDQKRVDALNDEIRQLQQENRQLLNERIKLEGIITRVETYL  
NENLRKRLDQVEQELNELRETEGGTVLTATTSELEAINKRVKDTMARSEDLDNSIDKTE  
AGIKELQKSMERWKNMEKEHMDAINHDTKELEKMTNRQGMLLKKKEECMKKIRELGSL  
PQEA FEKYQTL SLKQLFRKLEQCNT ELKKYSHVNKKALDQFVNFSEQKEKLIK RQEELD  
RGYKSIMELMNVLELRKYEAIQLTFKQVSKNFSEVFQKLVPGGKATLVMKKGDVEGSQS

QDEGEESGESERGSQSSVPSVDQFTGVGIRVSFTGKQGEMREMQQLSGGQKSLV  
ALALIFAIQKCDPAPFYLFDEIDQALDAQHRKAVSDMIMELAVHAQFITTTFRPELLESAD  
KFYGVKFRNKVSHIDVITAEMAKDFVEDDTTHG

SEQ ID No:51

MAVTLDKDAYYRRVKRLYSNWRKGEDEYANVDAIVSVGVDEEIVYAKSTALQTWLFG  
YELTDTIMVFCDDKIIFMASKKKKVEFLKQIANTKGNENANGAPAITLLIREKNESNKSSFD  
KMIEAIKESKNGKKIGVFSKDKFPGEFMKSWNDCLNKEGFDKIDISAVVAYTIAVKEDGE  
LNLMKKAASITSEVFNKFFKERVMEIVDADEKVRHSLAESVEKAIEEKKYLAGADPSTV  
EMCYPPIIQSGGNYNLKFSSVSDKNHMHFGAITCAMGIRFKSYCSNLVRTLMVDPSQEV  
QENYNFLLQLQEELLKELRHGVKICDVYNAVMDVVKKQKPELLNKITKNLGFGMGIEFR  
EGSLVINSKNQYKLKKG MVFSINLGFSDLTNKEGKKPEEKTYALFIGD TVLVDEDEGPATV  
LTSVKKKVKNVGIFLKNEDEEEEEEEEKDEAEDLLGRGSRAALLTERTRNEMTAEKRRRA  
HQKELAAQLNEEAKRRLTEQKGEQQIQKARKSNVSYKNPSLMPKEPHIREMKIYIDKKY  
ETVIMPVFGIATPFHIATIKNISMVSVEGDYTYLRINFYCPGSALGRNEGNIFPNPEATFVKE  
ITYRASNIKAPGEQTPALNLQNAFRIIEVQKRYKTREAEKEKEGIVKQDSL VINL NRS  
NPKLDLYIRPNIAQKRMQGSLEAHVNGFRFTSVRGDKVDILYNNIKHALFQPCD GEMII  
VLHFHLKNAIMFGKKRHTDVQFYTEVGEITTDLGKHQHMHDRDDLYAEQMEREMRHLK  
KTA FKNFIEKVEALTKEELEFEVPFRDLGFNGAPYRSTCLLQPTSSALVNATEWPPFVVT  
LDEVELIHFERVQFHLKNFDMVIVYKDYSKKVTMINAIPVASLDPIKEWLNSCDLKYTEGV  
QSLNWT KIMKTIVDDPEGFFEQGGWSFLEPEGEGSDAEEGDSESEIEDET FNPS EDDY  
EEEEEDSDEDYSSEAEESDYSKESLGSEEEESGKDWDELEEEARKADRESRYEEEEEQ  
SRSMSRKRKASVHSSGRGSNRGSRHSSAPPKKKRK

SEQ ID No:52

MVVSKMNKDAQMRAAINQKLIETGERERLKELLRAKLIECGWKDQLKAHCKEVIKEKGL  
EHVTVDLVAEITPKGRALVPDSVKKELLQRIRTF LAQHASL

SEQ ID No:53

MAEVEETLKRQLSQKGVQGGIIVNTEGIPIKSTMDNPTTTQYASLMHSFILKARSTVRDID  
PQNDLTFLRIRSKKNEIMVAPDKDYFLVIQNPT E

SEQ ID No:54

MAAVGRVGSFGSSPPGLSSTYTGGPLGNEIASGNNGGAAAGDDEDGQNLWSCILSEVS  
TRRSKLPAGKNVLLLGEDGAGKTSIRKIQQIEEYKKGRGLELYLYLVNHDDEDRDDQTR  
CNVWILDGDLYHKGLLKFSLDAVSLKDTLVMMLVVDMSKPWTALDSLQKWASVVREHVD  
KLKIPPEEMKQMEQKLIRDFQEYVEPGEDFPASPQRRNTASQEDKDDSVVPLGADTL  
THNLGIPVLVCTKCDAISVLEKEHDYRDEHFDFFQSHIRKFCLRYGAALIYTSVKENKNI  
DLVYKYIVQKLYGFPYKIPAVVVEKDADFIPAGWDNDKKIGILHENFQTLKAEDNFEDIITK  
PPVRKFVHEKEIMAEDDQVFLMKLQSLLAKQPPTAAGRPVDASPRVPGGSPRTPNRSV  
SSNVASVSPIPAGSKKIDPNMKAGATSEGVLANFFNSLLSKKTGSPGGPGVSGGSPAG  
GAGGGSSGLPPSTKKSGQKPVLDVHAELDRITRKPVTVSPTTPTSPTEGEAS

SEQ ID No:55

MVCTCVEGDNQFIVTEIPHVRQLISGDGVGECRAATEGRTLILEGLEKAERNVLPVLN  
NLLNREMQLEDGRFLMSAERYDKLLRDHTKKELDSWKIVRVSENFVIALGLPVPRYS  
GNPLDPPLRSRQARDIYYLPFKDQLKLLYSIGANVSAEKVSQLLSFATTLCSQESSTLG  
LPDFPLDSLAAAVQILDSFPMMPIKHAIQWLYPYSILLGHEGKMAVEGVLRKFELQDSGS  
SLLPKEIVKVEKMMENHVSQASVTIRIADKEVTIK

SEQ ID No:56

MSASQDSRSRDNGPDGMEPEGVIESNWNEIVDSFDDMNLSESLLRGIYAYGFEEKPSAI  
QQRAILPCIKGYDVIAQAQSGTGKTATFAISILQQIELDLKATQALVLAPTRELAQQIQKVV  
MALGDYMGASCHACIGGTNVRAEVQKLQMEAPHIIVGTPGRVFDMLNRRYLSPKYIKM  
FVLDEADEMLSRGFKDQIYDIFQKLNSNTQVVLLSATMPSDVLEVTKKFMRDPILVKK  
EELTLEGIRQFYINVEREEWKDLTLCPLYETLTITQAVIFINTRRKVDWLTEKMHARDFTV  
SAMHGDMDQKERDVIMREFRSGSSRVLITDLLARGIDVQQVSLVINYLPTNRENYIH  
RIGRGGFRGFRKGVAINMVTEEDKRTLRIETFYNTSIEEMPLNVADLI

SEQ ID No:57

MDQCVTVERELEKVLHKFSGYGQLCERGLEELIDYTGGLKHEILQSHGQDAELSGTSL  
VLTQCCKRIKDTVQKLASDHKDIHSSVSRVGKAIDKNFSDISSVGIDGCWQADSQRLL  
NEVMVEHFFRQGMLDVAEELCQESGLSVDPSQKEPFVELNRILEALKVRVLRPALEWA  
VSNREMLIAQNSSLEFKLHRLYFISLLMGTTNQREALQYAKNFQPFALNHQKDIQVLM  
GSLVYLRQGIENSPYVHLLDANQWADICDIFTRDACALLGLSVESPLSVSFSAGCVALPA  
LINIKAVIEQRQCTGVWNQKDELPIEVDLGKKCWYHSIFACPILRQQTDDNNPPMKLVCG  
HIISRDALNKMFGSKLKCPCPMEQSPGDAKQIFF

SEQ ID No:58

MLGTGPAAATTAATTSSNVSVLQQFASGLKSRNEETRAKAAKELQHYVTMELREMSQE  
ESTRFYDQLNHHIFELVSSSDANERKGGILAIASLIGVEGGNATRIGRFANYLRNLLPSND  
PVVMEMASKAIGRLAMAGDTFTA EYVEFEVKRALEWLGADRNEGRRHAAVLVLR ELAI  
SVPTFFFQQVQPPFDNIFVAVWDPKQAIREGAVAALRACLITTTQREP KEMQKPQWYR  
HTFEEAEKGFDETLAKEKGMNRDDRIHGALLILNELVRISSEMEGERLREEMEEITQQQLV  
HDKYCKDLMGFGTKPRHITPFTSFQAVQPQQSNALVGLLGYSSHQGLMGFGTSPSPAK  
STLVESRCCRDLMEEKFDQVCQWVLKCRNSKNSLIQMTILNLLPRLA AFRPSAFTDTQY  
LQDTMNHVLSVCVKEKERTAAFQALGLLSVAVRSEFKVYLPRVLDIIRAALPPKDFAHKR  
QKAMQVDATVFTCISMLARAMGPGIQQDIKELLEPMLAVGLSPALTAVLYDL SRQIPQLK  
KDIQDGLLKMLSLVLMHKPLRHPGMPKGLAHQLASPGLTTLPEASDVGSITLALRTLGSF  
EFEGHSLTQFVRHCADHFLNSEHKEIRMEAARTCSRLLTPSIHLISGHAHVVSQTAVQV  
VADVLSKLLVVGITDPDPDIRYCVLASLDERFDAHLAQAE NLQALFVALNDQVFEIRELAI  
CTVGR LSSMNPAFVMPFLRKMLIQILTELEHSGIGRIKEQSARMLGHLVSNAPRLIRPYM  
EPILKALILKLKDPDPDPNPGVINNVLATIGELAQVSGLEMRKWVDELFIIMDMLQDSSLL  
AKRQVALWTLGQLVASTGYVVEPYRKYP TLLLEVLLNFLKTEQNGQTRREAIRVLGLLGA  
LDPYKHKNIGMIDQSRDASAVSLSESKSSQDSSDYSTSEMLVNMGNLPLDEFYP AVS  
MVALMRIFRDQSLSHHHTMVVQAITFIFKSLGLKCVQFLPQVMPTFLNVIRVCDGAIREF  
LFQQLGMLVSFVKSHIRPYMDEIVTLMREFWVMNTSIQSTIILLIEQIVVALGGEFKLYLPQ  
LIPHMLRVFMHDNSPGRIVSIKLLAAIQLFGANLDDYLHLLLPPIVKLFD APEAPLPSRKAA  
LETVDRLTESLDFTDYASRIIHPIVRTL DQSPELRSTAMDTLSSLVFQLGKKYQIFIPMVNK  
VLVRHRINHQR YDVLCRIVKGYTLADEEEDPLIYQHRMLRSGQG DALASGPVETGPMK  
KLHVSTINLQKAWGAARRVSKDDWLEWLRRLSLELLKDSSSPSLRSCWAL AQAYNPMA  
RDLFNAAFVSCWSELNEDQQDELIRSIELALTSQDIAEVTQTLLNLAEFMEHSDKGPLPL  
RDDNGIVLLGERAAKCRAYAKALHYKELEFQKGPTPAILES LISINNKLQQPEAAAGVLE  
YAMKHFGELEIQATWYEKLHEWEDALVAYDKKMDTNKDDPELMLGRMRCLEALGEWG  
QLHQQCCEKWTLVNDETQAKMARMAAAAAWGLGQWDSMEEYTCMIPRDTHDGAFY  
RAVLALHQDLFSLAQQCIDKARDLLDAELTAMAGESYSRAYGAMV SCHMLSELEEVIQY  
KLVPERREIRQIWWERLQGCQRIVEDWQKILMVRS LVSPHEDMRTWLKYASLCGKS  
GRLALAHKTLVLLLGVDPSRQLDHPLPTVHPQVTYAYMKNMWKSARKIDAFQHMQH FV  
QTMQQQAQHA IATEDQQHKQELHKL MARCFLKLGEWQLNLQGINESTIPKVLQYY SAA  
TEHDRSWYKAWHAWAVMNF EAVLHYKHQNQARDEKKLRHASGANITNATTAATTA  
TATTTASTE GSNSESEAESTENSPTPSPLQKKVTEDLSKTLLMYT VPAVQGFFRSISLSR

GNNLQDTRLRVLTWFDYGHWPDVNEALVEGVKAIQIDTWLQVIPQLIARIDTPRPLVGRL  
 IHQLLDIGRYHPQALIYPLTVASKSTTTARHNAANKILKNMCEHSNTLVQQAMMVSEELI  
 RVAILWHEMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAY  
 GRDLMEAEQWCRKYMKSGNVKDLTQAWDLYYHVFRISKQLPQLTSLELQYVSPKLL  
 MCRDLELAVPGTYDPNQPIIRIQSIAPSLQVITSKQRPRKLTLMGSNGHEFVLLKGHED  
 LRQDERVMQLFGLVNTLLANDPTSLRKNLSIQRYAVIPLSTNSGLIGWVPHCDTLHALIR  
 DYREKKKILLNIEHRIMLRMAPDYDHLTLMQKVEVFEHAVNNTAGDDLAKLLWLKSPSS  
 EVWFDRRTNYTRSLAVMSMVGILGLGDRHPSNLMLDRLSGKILHIDFGDCFEVAMTR  
 EKFPKIPFRLTRMLTNAMEVTGLDGNYRITCHTVMVLREHKDSVMAVLEAFVYDPLL  
 NWRLMDTNTKGNKRSRTRTDSYSAGQSVEILDGVELGEPAHKKTGTTVPESIHSFIGD  
 GLVKPEALNKKAIQIINRVRDKLTGRDFSHDDTLDVPTQVELLIKQATSHENLCQCYIGW  
 CFW

## SEQ ID No:59

RQAWHEVAAPSWRGARLVQSALRVWQVGPHVARERVIPFSSLLGFQRRVCVSCVAGS  
 AFSGPRLASASRSNGQGSALDHFLGFSQPDSSVTPCVPVAVSMNRDEQDVLLVHHPDM  
 PENSRLRVLLGAPNAGKSTLSNQLLGRKVPVSRKVHTTRCQALGVITEKETQVILLD  
 TPGIISPGKQKRHHLELSLLEDPWKSMESADLVVVLVDVSDKWTRNQLSPQLLRCLTKY  
 SQIPSVLVMNKVDCLKQKSVLLELTAALTEGVVNGKKLKMRAQAFHSHPGTHCPSPAVK  
 DPNTQSVGNPQRIGWPHFKEIFMLSALSQEDVKTLYLLTQAQPGPWEYHSAVLTSQ  
 TPEEICANIIREKLEHLPQEVYNVQKTAWEEGPGGELVIQKLLVPKESYVKLLIGP  
 KGHVISQIAQEAGHDLMDIFLCDVDIRLSVKLLK

## SEQ ID No:60

MAYSQGGGKKKVCYYYDGDIGNYYYGQGHMPKPHRIRMTHNLLLNYGLYRKMEIYRP  
 HKATAEEMTKYHSDEYIKFLRSIRPDNMSEYSKQMHIFNVGEDCPAFDGLFEFCQLSTG  
 GSVAGAVKLNRRQQTDMAVNWAGGLHHAKKYEASGFCYVNDIVLAILELLKYHQRVLYID  
 IDIHHGDGVVEAFYTTDRVMTVSFHKYGEYFPGTGDLRDIGAGKGKYYAVNFPMCDGID  
 DESYGQIFKPIISKVMEMYQPSAVVLQCGADSLSGDRLGCFNLTVKGHAKCDEVVKTFN  
 LPLLMLGGGGYTIRNVARCWTYETAVALDCEIPNELPYNDYFEYFGPDFKLHISPSNMT  
 NQNTPEYMEKIKQRLFENLRMLPHAPGVQMQAIPEDAVHEDSGDEGEDPDKRISIRA  
 SDKRIACDEEFSDSEDEGEGGRRNVADHKKGAKKARIEEDKKETEDKKTVDVKEEDKSK  
 DNSGEKTDTKGKSEQLSNP

SEQ ID No:61

MPSESFCLAAQARLDSKWLKTDIQLAFTRDGLCGLWNEMVKDGEIVYTGTESTQNGEL  
PPRKDDSVESPGTKKEDLNDKEKKDEEETPAPIYRAKSILDSWVWGKQPDVNELKECL  
SVLVKEQQALAVQSATTTLSALRLKQRLVILERYFIALNRTVFQENVKVWKSSGISLPP  
VDKKSSRPAGKGVEGLARVGSRAALSFAFAFLRRAWRSGEDADLCSELLQESLDALRA  
LPEASLFDESTVSSVWLEVVERATRFLRSVVTGDVHGTPATKGPGSIPLQDQHLALAILL  
ELAVQRGTLSQMLSAILLLLQLWDSGAQETDNERSAQGTSAPLLPLLQRFQSIICRKDAP  
HSEGDMHLLSGPLSPNESFLRYLTLPQDNELALDLRQTAVVMAHLDRLATPCMPPLCS  
SPTSHKGSLEQEVIGWGLIGWKYYANVIGPIQCEGLANLGVTTIACAERFLILSRNGRVY  
TQAYNSDTLAPQLVQGLASRNIVKIAAHSDGHHYLAATGEVYSWGCDDGGRLGHGD  
TVPLEEPKVISAFSGKQAGKHVVHIACGSTYSAAITAEGELYTWGRGNYGRLGHGSSSED  
EAIPMLVAGLKGLKVIDVACGSGDAQTLAVTENGQVWSWGDGDYDKLGRGGSDDGCKT  
PKLIEKLQDLDDVVKVRCGSQFSIALTKDGQVYSWGKGDNQRLLGHGTEEHVRYPKLLEG  
LQGGKVIDVAAGSTHCLALTEDSEVHSWGSNDQCQHFDTLRVTKPEPAALPGLDTKHIV  
GIACGPAQSFAWSSCSEWSIGLRVPFVVDICSMTFEQLDLLLLRQVSEGMDGSADWPPP  
QEKECVAVATLNLRLQLHAAISHQVDPEFLGLGLGSILLNSLKQTVVTLASSAGVLSTV  
QSAAQAVLQSGWSVLLPTAEERARALSALLPCAVSGNEVNISPGRRFMIDLLVGSMLAD  
GGLESALHAAITAEIQDIEAKKEAQKEKEIDEQEANASTFHRSRTPDKDLINTGICSSG  
KQCLPLVQLIQQLLRNIASQTVARLKDVARRISSCLDFEQHSRERSASLDWLLRFQRLLI  
SKLYPGESIGQTSDISSPELMGVGSLLKKYTALLCTHIGDILPVAASIASTSWRHFAEVAYI  
VEGDFTGVLLPELVVSIVLLLSKNADLMQEAGAVPLLGGELLEHLDRFNHLAPGKERDDH  
EELAWPGIMESFFTQGNCRNNEEVTILRKADLENHNKDGGFVTVIDGKVYDIKDFQTQS  
LTGNSILAQFAGEDPVVALEAALQFEDTRESMHAFQVGVQYLEPDQEIVTIPDLGSLSSPLI  
DTERNLGLLLGLHASYLAMSTPLSPVEIECAKWLQSSIFSGGLQTSQIHRYNEEKDED  
HCSSPGGTPASKSRLCSHRRALGDHSQAFLQAIADNNIQDHNKDFLCQIERYCRQCH  
LTPMIFPPEHPVEEVGRLLLCCLLKHEDLGHVALSLVHAGALGIEQVKHRTLPSKVVDV  
CRVVYQAKCSLIKTHQEQRYSYKEVCAPVIERLRFLFNLRPVAVCNDLSIMSKFKLLSSL  
PRWRRIAQKIIERRRKKRVPKKPESMDDEEKIGNEESDLEEACILPHSPINVDKRPIA  
PKDKWQPLLSTVTGVHKKYKWLKQNVQGLYPQSPLLSTIAEFALKEEPVDVEKMRKCLL  
KQLERAQVRLEGIDTILKLASKNFLLPSVQYAMFCGWQRLIPEGIDIGEPLTDCLKDVDLI  
PPFNRMILLEVTFGKLYAWAVQNIRNVLMDASATFKELGIQPVPLQTITNENPSGPSLGTI  
PQARFLLVMLSMMLTLQHGANNLDLLLNSGMLALTQTALRLIGPSCDNVEEDMNASAAQ  
ASATVLEETRKETAPVQLPVSGPELAAMMKIGTRVMRGVDWKWGDQDGGPPGLGRVI  
GELGEDGWIRVQWDTGSTNSYRMGKEGKYDLKLAELPAAQPSAEDSDTEDDSEAEQ

TERNIHPTAMMFTSTINLLQTLCLSAGVHAEIMQSEATKTLCGLLRMLVESGTTDKTSSP  
NRLVYREQHRSWCTLGFVRSIALTPQVCGALSSPQWITLLMKVVEGHAPFTATSLQRQI  
LAVHLLQAVLPWDKTERARMDKCLVEKLFDFLGSLTTCSSDVPLLRESTLRRRRVRP  
QASLTATHSSTLAEVVALRLHSLTQWNGLINKYINSQLRSITHSFVGRPSEGAQLED  
YFPDSENPEVGGLMAVLAVIGGIDGRLRLGGQVMHDEFEGGTVTRITPKGKITVQFSDM  
RTCRVCPLNQLKPLPAVAFNVNNLPFTEPMLSVAQLVNLASGSKLEKHKIKSTKQAF  
GQVDLDLLRCQQLKLYILKAGRALLSHQDKLRQILSQPAVQETGTVHTDDGAVVSPDLG  
DMSPEGPQPPMILLQQLLASATQPSPVKAIFDKQELEAAALAVCQCLAVESTHPSSPGF  
EDCSSSEATTPVAVQHIHPARVKRRKQSPVPALPIVVQLMEMGFSRRNIEFALKSLTGA  
SGNASSLPGVEALVGWLLDHSDIQVTELSADTVSDEYSDEEVVEDVDDAAYSMSTGA  
VVTESQTYKKRADFLSNDDYAVYVRENIQVGMVRCRAYEREEVCEGDVGKVIKLRD  
LHDLNVQCDWQQKGGTYWVRYIHVELIGYPPSSSSSHIKIGDKVRVKASVTTPKYKWG  
SVTHQSVGVVKAFSANGKDIIVDFPQQSHWTGLLSEMELVPSIHPGVTCDGCMFPING  
SRFKCRNCDDDFCETCFKTKKHNRHTFGRINEPGQSAVFCGRSGKQLKRCHSSQP  
GMLDSWSRMVKSINVSSSVNQASRLIDGSEPCWQSSSGSQGKHWRLEIFPDVLVHRL  
KMIVDPADSSYMPSLVVVSGGNSLNNLIELKTININPSDTTVPLLNDYTEYHRYEIAIKQC  
RSSGIDCKIHGLILLGRIRAEEDLAAPFLASDNEEEDEKGNSSGLIRKKAAGLESAAT  
IRTKVFVWGLNDKDQLGGLKGSKIKVPSFSETLSALNVVQVAGGSKSLFAVTVEGKVYA  
CGEATNGRLGLGISSGTVPIPRQITALSSYVVKVAVHSGGRHATALTVDGKVFSWGEG  
DDGKLGHFSRMNCDKPRLEALKTKRIRDIACGSSSHAALTSSGELYTWGLGEYGRGLH  
GDNTTQLKPKMVKVLGHRVIQVACGSRDAQTLALTDEGLVFSWGDGDFGKLGRGGS  
EGCNIPQNIERLNGQGVQCIECGAQFSLATKSGVVWTWGKG DYFRLGHGSDVHVRK  
PQVVEGLRGKKIVHAVGALHCLAVTDSGQVYAWGDNDHGQQGNGTTTVNRKPTLVQ  
GLEGQKITRVACGSSHSVAWTTVDVATPSVHEPVLFQTARDPLGASYLGVPDADSSA  
ASNKISGASNSKPNRPSLAKILLSLDGNLAKQQALSHILTALQIMYARDAVVGALMPAAMI  
APVECPSFSSAAPSASAMASPMNGEELAVDIEDRLSPNPWQEKREIVSSEDAVTP  
SAVTPSAPSASARPFIPVTDDLGAASIIAETMTKTKEDVESQNKAAGPEPQALDEFTSLI  
ADDTRVVVDLLKLSVCSRAGDRGRDVL SAVLSGMGTAYPQVADM LLELCVTELEDVAT  
DSQSGRLSSQPVVVESSHYPYTD TSTSGTVKIPGAEGLRVEFDRQCSTERRHDPLTVM  
DGVNRIVSVRSGREWSDWSSEL RIPGDELKWKFISDGSVNGWGW RFTVYPIMPAAGP  
KELLSDRCVLSCPSMDLVTCLLD FRLNLASNRSIVPRLAASLAACAQLSALAASHRMWA  
LQRLRKLLTTEFGQSININRL LGENDGETRALSFTGSALAALVKGLPEALQRQFEYEDPI  
VRGGKQLLHSPFFKVLVALACDLELDTLPCCAETHKWAWFRRYCMASRVAVALDKRTP  
LPRLFLDEVAKKIRELMADSENMDVLHESHDFKREQDEQLVQWMNRRPDDWTLSAG

GSGTIYGWGHNHRGQLGGIEGAKVKVPTPCALATLRPVQLIGGEQTLFAVTADGKLYA  
 TGYGAGGRLGIGGTESVSTPTLLESIQHVFIIKKVAVNSGGKHCLALSSEGEVYSWGEAE  
 DGKLGHGHRSPCDRPRVIESLRGIEVVDVAAGGAHSACVTAAGDLYTWGKGRYGRLG  
 HSDSEDQLKPKLVEALQGHRVVDIACGSGDAQTLCLTDDDTVWSWGDGDYGKLGRG  
 GSDGCKVPMKIDSLTGLGVVKVECGSQFSVALTKSGAVYTWGKGDYHRLGHGSDDHV  
 RRPRQVQGLQGKKVIAIATGSLHCVCCTEDGEVYTWGDNDEGQLGDGTTNAIQRPRLV  
 AALQGKKVNRVACGSAHTLAWSTSKPASAGKLPAQVPMEYNHLQEIPIALRNRLLLH  
 HLSELFPCPCIPMFDLEGLDETGLGPSVGFDTLRGILISQGKEAAFRKVQATMVRDRQ  
 HGPVVELNRIQVKRSRSKGGLAGPDGTSVFGQMCAMSSFGPDSLLLPHRVWKVKF  
 VGESVDDCGGGYSESIAEICEELQNGLTPLLIVTPNGRDESGANRDCYLLSPAARAPVH  
 SSMFRFLGVLLGIAIRTSPLSLNLAEPVWKQLAGMSLTIALDLSEVDKDFIPGLMYIRDNE  
 ATSEEFAMSLPFTVPSASGQDIQLSSKHHTITLDNRAEYVRLAINYRLHEFDEQVA AVR  
 EGMARVVPVPLLSLFTGYELETMVCGSPDIPLHLLKSVATYKGIEPSASLIQWFWWEVME  
 SFSNTERSLFLRFVWGRTRLPRTIADFRGRDFVIQVLDKYNPPDHFLPESYTCFFLLKLP  
 RYSCKQVLEEKLYAIHFCKSIDTDDYARIALTGEPAAADDSSDDSDNEDVDSFASDSTQ  
 DYLTDGH

SEQ ID No:62

MICTFLRAVQYTEKLHRSSAKRLLLPYIVLNKACLKTEPSLRCLQYQKKTLRPRCILGVT  
 QKTIWTQGPSRKAKEDGSKQVSVHRSQRGGTAVPTSQKVKEAGRDFTYLIVVLFGISI  
 TGGLFYTIFKELFSSSSPSKIYGRALEKCRSHPEVIGVFGESVKGYGEVTRRGRQRHVR  
 FTEYVKDGLKHTCVKFYIEGSEPGKQGTVYAQVKENPGSGEYDFRYIFVEIESYPRRTIII  
 EDNRSQDD

SEQ ID No:63

MAATSGTDEPVSGELVSVAHALSPLAESYGNDPDIEMAWAMRAMQHAEVYYKLISVD  
 PQFLKLTKVDDQIYSEFRKNFETLRIDVLDPEELKSESAKEKWRPFCLKFNGIVEDFNYG  
 TLLRLD

SEQ ID No:64

MRNLKLFRTLEFRDIQGPGNPQCFSLRTEQGTVLIGSEHGLIEVDPVSREVKNEVSLVA  
 EGFLPEDGSGRIVGVQDLLDQESVCVATASGDVILCSLSTQQLECVGSGVASGISVMSW  
 SPDQELVLLATGQQTLIMMTKDFEPILEQQIHQDDFGESKFITVGWGRKETQFHGSEGR  
 QAAFQMQMHESALPWDDHRPQVTWRGDGQFFAVSVVCPETGARKVRVWNREFALQ

STSEPVAGLGPALAWKPSGSLIASTQDKPNQQDIVFFEKNGLLHGHFTLPFLKDEVKVN  
 DLLWNADSSVLAVRLEDLQREKSSIPKTCVQLWTVGNYHWYKQSLSFSTCGKSKIVSL  
 MWDPVTPYRLHVLQCGWHYLAJDWHWTDRSVGDNSSDLNVAVIDGNRVLVTVFR  
 QTVVPPPMCTYQLLFFHPVNQVTFLAHPQKSNDLAVLDASNQISVYKCGDCPSADPTV  
 KLGAVGGSGFKVCLRTPHLEKRYKIQFENNEDQDVNPLKLGLLTWIEEDVFLAVSHSEF  
 SPRSVIHHLTAASSEMDEEHGQLNVSSSAAVDGVIIISLCCNSKTKSVVLQLADGQIFKYL  
 WESPSLAIKPWKNSGGFPVRFPYCTQTELAMIGEEECVLGLTDRCRFFINDIEVASNIT  
 SFAVYDEFLLLTTHSHTCQCFCRLRDASFCTLQAGLSSNHVSHGEVLRKVERGSRIVTVV  
 PQDTKLVLQMPRGNLEVHHRALVLAQIRKWLDKLMFKEAFECMRKLRINLNPIYDHNP  
 KVFLGNVETFIKQIDSVNHINLFFTELKEEDVTKTMYAPVTSSVYLSRDPDGNKIDLVCD  
 AMRAVMESINPHKYCLSILTSHVKKTTPELEIVLQKVHELQGNAPSDPDVSAEEALKYL  
 LHLVDVNELYDHS LGTYDFDLVLMVAEKSQKDPKEYLPFLNTLKKMETNYQRFTIDKYL  
 KRYEKAIGHLSKCGPEYFPECLNLIKDKNLYNEALKLYSPSSQQYQDISIAYGEHLMQE  
 MYEPAGLMFARCGAHEKALSAFLT CGNWKQALCVAAQLNFTKDQLVGLGRTLAGKLV  
 EQRKHIDAAMVLEESAQDYEEAVLLLLLEGAAWEEALRLVYKYNRLDIETNVKPSILEAQ  
 KNYMAFLDSQTATFSRHKKRLLVRELKEQAQQAGLDDEVPHGQESDLFSETSSVVSG  
 SEMSGKYSHSNSRISARSSKNRRKAERKKHSLKEGSPLEDLALLEALSEVVQNTENLKD  
 EVYHILKVLFLFEFDEQGRELQKAFEDTLQLMERSLPEIWTLYQQNSATPVLGPNSTAN  
 SIMASYQQQKTSVPVLD AELFIPPKINRRTQWKLSLLD

SEQ ID No:65

MVQKKKFCPRLLDYLIVGARHPSSDSVAQTPELLRRYPLEDHTEFPLPPDVVFFCQPE  
 GCLSVRQRRMSLRDDTSFVFTLTDKDTGVTRYGICVNFYRSFQKRISKGKGEGGAGSR  
 GKEGTHATCASEEGGTESSESGSSLQPF SADSTPDVNQSPRGKRRAKAGSRSRNSTL  
 TSLCVLSHYPPFFSTFRECLYTLKRLVDCCSERLLGKKLGIPRGVQRDTMWRIFTGSLLE  
 EKSSALLHDLREIEAWIYRLLRSPVPVSGQKRVDIEVLPQELQPALTFALPDPSRFTLVDF  
 PLHLPELLGVDAQLLLTCILLEHKVVLQSRDYNALSMSVMAFVAMIYPLEYMFVPIPL  
 PTCMASAEQLLLAPTPYIIGVPASF FLYKLDFKMPDDVWLVDLDSNRVIAPTNAEVLPILP  
 EPESLELKKHLKQALASMSLNTQPILNLEKFHEGQEIPLLLGRPSNDLQSTPSTEFNPLIY  
 GNDADSDVDVATRVAMVRFFNSANVLQGFQMHTRTLRLFP RPVVAFAQGSFLASRPRQ  
 TPFAEKLARTQAVEYFGEWILNPTNYAFQRIHNNMFDPALIGDKPKWYAHQLQPIHYRV  
 YDSNSQLAEALSVPPERDSDSEPTDDSGSDSMDYDDSSSSYSSLGDFVSEMMKCDIN  
 GDTPNVDPLTHAALGDASEVEIDELQNQKEAE EPGPDSSENSQENPPLRSSSSTTASSS  
 PSTVIHGANSEPADSTEMDDKAAVGVSKPLPSVPPSIGKSNVDRRQAEIGEGSVRRRIY

DNPYFEPQYGFPPEEDEDEQGESYTPRFSQHVSGNRAQKLLRPNSLRLASDSAESD  
SRASSPNSTVSNSTSTEGFGGIMSFASSLYRNHSTSFSLSNLTLPTKGAREKATPFPPLK  
VFGLNTLMEIVTEAGPGSGEGNRRALVDQKSSVIKHSPTVKREPPSPQGRSSNSSENQ  
QFLKEVVHVSVDGQGVGWLNMKKVRRLLLESEQLRVFVLSKLNRMVQSEDDARQDIIPD  
VEISRKVYKGM DLLKCTVLSLEQSYAHAGLGGMASIFGLLEIAQTHYYSKEPDKRKRSP  
TESVNTPVGKDPGLAGRGDPKAMAQLRVPQLGPRAPSATGKGPKELDTRSLKEENFIA  
SIELWNKHQEVKKQKALEKQRPEVIKPVFDLGETEEKKSQISADSGVSLTSSSQRTDQD  
SVIGVSPAVMIRSSSQDSEVSTVVSNSSETLGADSDLSSNAGDGPGGEGSVHLASSR  
GTLSDSEIETNSATSTIFGKAHSLKPCIKEKLAGSPIRTSEDVSQRVLYEGLLGRDKGS  
MWDQLEDAAMETFSISKERSTLWDQM QFWEDAF L DAVMLEREGMGMDQGPQEMIDR  
YLSLGEHDRKRLEDDERLLATLLHNLISYMLLMKVNKN DIRKKVRRLMGKSHIGLVYSQ  
QINEVLDQLANLNGRDLSIWSSGSRHMKKQTFVVHAGTDTNGDIFFMEVCCDCVVLRS  
NIGTVYERWWWYK LINMTYCPKTKVLCLWRRNGSETQLNKFYTKKCRELYYCVKDSME  
RAAARQQSIKPGPELGGEFPVQDLKTGEGGLLQVTLEGINLKFMHNQVFIELNHIKKCNT  
VRGVFVLEEFVPEIKEV VSHKYKTPMAHEICYSVLCLFSYVA AVHSSEEDLRTPPRPVSS

SEQ ID No:66

AAASRCPGIMVALRGLGSGLQPWCPDLRLLEWVDTVWELDFTETEP LDPSIEAEI IETGL  
AAFTKLYESLLPFATGEHGSMESIWTFFIENNVSHSTLVALFYHFVQIVHKKNVSVQYRE  
YGLHAAGLYFLLLEVPGSVANQVFHPVMFDKCIQTLKKSWPQESNLNRKRKKEQPKSS  
QANPGRHRKRKGKPPREDIEMDEIIEEQEDENICFSARDLSQIRNAIFHLLKNFLRLLPKF  
SLKEKPQCVCQNCIEVFVSLTNFEPVLHECHVTQARALNQAKYIPELAYYGLYLLCSPIHG  
EGDKVISCVFHQMLSVILMLEVGEGSHRAPLAVTSQVINCRNQAVQFISALVDELKESIF  
PVVRILLQHICAKVVDKSEYRTFAAQLSVQLLSKLPCGEYAMFIAWLYKYSRSSKIPHRV  
FTLDVVLALLELPEREVDNTLSLEHQKFLKHKFLVQEIMFDRCLDKAPT VRSKALSSFAH  
CLELTVTSASESILELLINSPTFSVIESHPGTLLRNSSAFSYQRQTSNRSEPSGEINIDSSG  
ETVGSGERCVMAMLR RRIRDEKTNVRKSALQVLVSILKHCDVSGMKEDLWILQDQCRD  
PAVSVRKQALQSLTELLMAQPRCVQIQKAWLRGVVPVVMDCESTVQEKALEFLDQLLL  
QNIRHHSHFHSGDDSQVLAWALLTLLTTESQELSRYL NKA FHIW SKKEKFSPTFINNVIS  
HTGTEHSAPAWMLLSKIAGSSPRLDYSRIIQSWEKISSQQNPNSNTLGHILCVIGHIAKHL  
PKSTRDKVTD AVKCKLNGFQWSLEVISSAVDALQRLCRASAETPAEEQELLTQVCGDV  
LSTCEHRLSNIVLKENG TGNMDEDLLVKYIFTLG DIAQLCPARVEKRIFLLIQSVLASSAD  
ADHSPSSQGSSEAPASQPPPQVRGSVMPSVIRAHAIITLGKLC LQHEDLAKKSIPALVRE  
LEVCEDEVAVRNNVIIVMCDLCIRYTIMVDKYIPNISMCLKDSDPFIRKQTLILLTNLLQEEFV

KWKGS�FFRFVSTLIDSHPDIA SFGEFCLAHLLLKRNPMFFQH FIECIFHFNNYEKHEKY  
 NKFPQSEREKRLFSLKGKSNKERRMKIYKFLL EHFTEQRFNITSKICLSILACFADGILPL  
 DLDASELLSDTFEVLSSKEIKLLAMRSKPKDLLMEEDDMALANVVMQEAQKKLISQVQ  
 KRNFIENIPIIISLKT VLEKNKIPALRELMHYLREVMQDYRDELKDFFAVDKQLASELEYD  
 MKKYQEQLVQE QELAKHADVAGTAGGAEVAPVAQVALCLETVPVPAGQENPAMSPAV  
 SQPCTPRASAGHVAVSSPTPETGPLQRLLPKARPM SLSTIAILNSVKKAVESKSRHRSR  
 SLGVLPFTLN SGSP EKTCSQVSSYSLEQESNGEIEHVTKRAISTPEKSISDVTFGAGVSYI  
 GTPRTPSSAKEKIEGRSQGNDILCLSLPDKPPPQPQQWNVRSPARNKDT PACSRRSLR  
 KTPLKTAN

SEQ ID No:67

MWNDIELLTND DTGSGYLSVGSRKEHGTALYQVDLLVKISSEKASLNPKIQACSLSDGFI  
 IVADQSVILLDSICRSLQLHLVFDTEVDVVG L CQEGKFLLVGERSGNLHLIHVTSKQTLT  
 NAFVQKANDENRR TYQNLVIEKDGSNEGTY YMLLLTYSGFFCITNLQLLKIQQA IENVDF  
 STAKKLQGQIKSSFISTENYHTLGCLSLVAGDLASEVPVIIGGTGNCAFSKWE PDSSKKG  
 MTKVKNLIDAEI IKGAKKFQLIDNLLFVLDTDNVLSLWDIYTLPVWNWPSLHV EEFLLTTE  
 ADSPSSVTWQGITNLKLIALTASANKKMKNLMVYSLPTMEILYSLEVSSVSSLVQTGISTD  
 TIYLLEGVCKNDPKLSEDSVSVLVLRCLTEALPENRLSRLLHKHRFAEAE SFAIQFGLDV  
 ELVYKVKSNHILEKLALSSVDASEQTEWQQLVDDAKENLHKIQDDEFV VNYCLKAQWIT  
 YETTQEMLNYAKTRLLKKEDKTALIYSDGLKEVLRAHAKLTTFYGA FGPEKFSGSSWIEF  
 LNNEDDLKDIFLQLKEGNL VCAQYLWLRHRANFESRFDVKMLESLLNSMSASVSLQKLC  
 PWFKN DVIPFVRRTVPEGQIILAKWLEQAARNLELTDKANWPENGLQLAEIFFTA EKTDE  
 LGLASSWHWISLKD YQNT EEV CQLRTL VNNLRELITLHRKY NCKLALSDFE KENTTTTIVF  
 RMFDKVLAPELIPSILEKFIRVYMREHDLQEEELLLLYIEDLLNRCSSKSTSLFETAWEAK  
 AMAVIACLSDTDLIFDAVLKIMYAAVVPWSAAVEQLVKQHLEMDHPKV KLLQESYKLME  
 MKKLLRGYGIREVNLLNKEIMRVVRYILKQDVPSSLEDALKVAQAFMLSDDEIYSLRIIDLI  
 DREQGEDCLLLLKSLPPAEAEKTAERVIIWARLALQEEP DHSKEGKAWRMSVAKTSVDI  
 LKILCDIQKDNLQKKDECEEM LKLFKEVASLQENFEVFLSFEDYSNSSLVADLREQHIKA  
 HEVAQAKHKPGSTPEPIAAEVRSPSMESKLHRQALALQMSKQELEAE LTLRALKDGNIK  
 TALKKCSDLFKYHCNADTGKLLFLT CQKLCQMLADNVPVTVPVGLNLPSMIHDLASQAA  
 TICSPDFLLDALELCKHTLMAVELSRQCQMDDCGILMKASFGTHKDPYEEWSYS DFFSE  
 DGIVLESQMVLVPVIYELISSLVPLAESKRYPLESTSLPYCSLNEGDGLVLPVINSISALLQN  
 LQESSQWELALRFVVG SFGTCLQHSVS NF MNATLSEKLFGETTLVKSRHVVMELKEKA  
 VIFIRE NATTLHKVFNCRLVDLDLALGYCTLLPQKDV FENLWKLIDKAWQNYDKILAISLV

GSELASLYQEIEMGLKFRELSTDAQWGIRLGKLGISFQPVFRQHFLTCKDLIKALVENID  
MDTSLILEYCSTFQLDCDAVLQLFIETLLHNTNAGQQGQGDASMDSAKRRHPKLLAKALE  
MVPLLTSTKDLVISLSGILHKLDPYDYEMIEVVVKVIERADEKITNININQALSILKHLKSYR  
RISPPVDLEYQYMLEHVITLPSAAQTRLPPHLLFFGTAQNFWKILSTELSEESFPTLLLISK  
LMKFSLDTLYVSTAKHVFEKKLKPCLLTQAKSSTLINKEITKITQTIESCLLSIVNPEWAV  
AIAISLAQDIPEGSEFKISALKFCLYLAERWLQNIPSQDEKREKAEALLKKLHIQYRRSGTEA  
VLIAHKLNTEEYLRVIGKPAHLIVSLYEHP SINQRIQNSSGTDYPDIHAAAKEIAEVNEINLE  
KVWDMLEKWLCPSTKPGKEKPSSELFELQEDEALRRVQYLLLSRPIDYSSRMLFVFATST  
TTTLGMHQLTFAHRTRALQCLFYLADEKTESLFKKPIEEVKSYLRCITFLASFETLNIPITY  
ELFCSSPKEGMIKGLWKNHSHESMAVRLVTELCLEYKIYDLQLWNGLLQKLLGFNMIPY  
LRKVLKAISIIHSLWQVPYFSKAWQRVIIQIPLLSASCPLSPDQLSDCSESLIAVLECPVSG  
DLDLIGVARQYIQLELPAFALACLMLMPHSEKRHHQIKNFLGSCDPQVILKQLEEHMNTG  
QLAGFSHQIRSLILNNIINKKEFGILAKTKYFQMLKMHAMNTNNITELVNYLANDLSLDEA  
SVLITEYSKHCGKPVPPDTAPCEILKMFLSGLS

SEQ ID No:68

MSEPGGGGGEDGSAGLEVSQNVADVSVLQKHLRKLVPPLLEDGGEAPAALEAALEE  
KSALEQMRKFLSDPQVHTVLVERSTLKEDVGDEGEEKEFISYNINIDIHYGVKSNSLAFI  
KRTPVIDADKPVSSQLRVLTLSSESPYETLHSHFISNAVAPFFKSYIRESGKADRDGDKMA  
PSVEKKIAELEMGLLHLQQNIEIPEISLPIHPMITNVAKQCYERGEKPKVTDGDKVEDPT  
FLNQLQSGVNRWIREIQKVTCLDRDPASGTALQEISFWLNLERALYRIQEKRESPEVLLT  
LDILKHGKRFHATVSFDTDTGLKQALETVNDYNPLMKDFPLNDLLSATELTKIRQALVAIF  
THLRKIRNTKYPIQRALRLVEAISRDLSQLLKVLGTRKLMHVAYEEFEKVMVACFEVFQ  
TWDDEYEKLQVLLRDIVKRKREENLKMVWRINPAHRKLQARLDQMRKFRRQHEQLRA  
VIVRVLRPQVTAVAQQNQGEVPEPQDMKVAEVLFDAADANAIEEVNLAYENVKEVDGL  
DVSKEGTEAWEAAMKRYDERIDRVETRITARLRDQLGTAKNANEMFRIFSRFNALFVRP  
HIRGAIREYQTQLIQRVKDDIESLHDKFKVQYPQSQACKMSHVRDLPPVSGSIIWAKQID  
RQLTAYMKRVEDVLGKGWENHVEGQKLKQDGDSFRMKLNTQEIFDDWARKVQQRN  
GVSGRIFTIESTRVRGRTGNVLKLVNFLPEIITLSKEVRNLKWLGRVPLAIVNKAHQAN  
QLYPFAISLIESVRTYERTCEKVEERNTISLLVAGLKKEVQALIAEGIALVWESYKLDPYV  
QRLAETVFNQEKVDDLLIIEEKIDLEVRSLCTMYDHKTFSEILNRVQKAVDDLNLHSYS  
NLPIWVNKLDMEIERILGVRLQAGLRAWTQVLLGQAEDKAEVDMDTDAPQVSHKPGGE  
PKIKNVVHELRTNQVIYLNPPIEECRYKLYQEMFAWKMVVLSLPRIQSQRVQGVHYEL  
TEEEKFYRNALTRMPDGPVAALESYSAVMGIVSEVEQYVKVWLQYQCLWDMQAENIY

NRLGEDLNKWQALLVQIRKARGTFDNAETKKEFGPVVIDYGKVQSKVNLKYDSWHKEV  
LSKFGQMLGSNMTEFHSSQISKSQRQEQHSVDTASTSDAVTFITYVQSLKRRIKQFEKQ  
VELYRNGQRILLEKQRFQFPPSWLYIDNIEGEWGAFNDIMRRKDSAIQQQVANLQMKIV  
QEDRAVESRTDLLTDWEKTKPVTGNLRPEEALQALTIYEGKFGRLKDDREKCAKAKEA  
LELTDGLLSGSEERVQVALEELQDLKGVWSEL SKVWEQIDQMKEQPWVSVQPRKLR  
QNL DALLNQLKSFPARLRQYASYEFVQRLLKGYM KINMLVIELKSEALKDRHWKQLMKR  
LHVNWVVSELTLGQIWDVDLQKNEAIVKDVLVAQGEMALEEFLKQAKVWNTYELDLV  
NYQNK CRLIRGWDDL FNKVKEHINSVSAMKLS PYYKVFEEDALSWEDKLN RIMALFDV  
WIDVQRRWVYLEGIFTGSADIKHLLPVETQRFQSISTEFLALMKKVSKSPLVMDVLNIQG  
VQRSLERLADLLGKIQKALGEYLERERSSFP RFYFVGDEDLLEIIGNSKNVAKLQKHFKK  
MFAGVSSIILNEDNSVVLGISSREGEV MFKTPVSITEHPKINEWLTLVEKEMRVTLAKLL  
AESVTEVEIFGKATSIDPNTYITWIDKYQAQLVVL SAQIAWSENVETALSSMGGGGDAAP  
LHSVLSNVEVT LNVLADSVLMEQPPLRRRKLEHLITELVHQRDVTRSLIKSKIDNAKSFE  
WLSQMRFYFDPKQTDVLQQLSIQMANAKFN YGFEYLGVDKLVQTPLTDRCYLTMTQA  
LEARLGGS PFPGAGTGKTESVKALGHQLGRFVLVFNCDETFDFQAMGRIFVGLCQVGA  
WGCDFDEFNRLEERM LSAVSQQVQCIEALREHSNP NYDKTSAPITCELLNKQVKVSPD  
MAIFITMNP GYAGRSNL PDNLKKLFRSLAMTKPDRQLIAQVMLYSQGFRTAEVLANKIVP  
FFKLCDEQLSSQS SHYDFGLRALKSVLVSAGNVKRERIQKIKREKEERGEAVDEGEIAEN  
LPEQEILIQSVCETMVPKLVAEDIPLLFSLLSDVFPGVQYHRGEMTALREELKKVCQEMY  
LTYGDGEEVGGMWVEKVLQLYQITQINHGLMMVGP SGSGKSM AWRVLLKALERLEGV  
EGVAHIIDPKAISKDHLYGTLDPNTREWTDGLFTHVLRKIIDSVRGELQKRQWIVFDGDV  
DPEWVENLNSVLDDNKLLTLPNGERLSLPPNVRIMFEVQDLKYATLATVSRGMMVWFS  
EDVLSTDMIFNNFLARLRSIPLDEGEDEAQR RRKGKEDEGEEAASPMLQIQRDAATIMQ  
PYFTSNGLVTKALEHAFQLEHIMDLTRLRCLGSLFSMLHQACRNVAQYNANHPDFPMQI  
EQLERYIQRYLVYAILWSLSGDSRLKMRAELGEYIR RITTVPLPTAPNIPIIDYEVSISGEW  
SPWQAKVPQIEVETHKVAAPDVVPTLDTVRHEALLYTWLAEHKPLVLCGPPGSGKTM  
TLFSALRALPDMEVWGLNFSSATTPELLLKTFDHYCEYRRTPNGVV LAPVQLGKWLVL F  
CDEINLPDMDKYGTQRVISFIRQMVEHGGFYRTSDQ TWVKLERIQFVGACNPPTDPGR  
KPLSHRFLRHVPV VYVDYPGPASLTQIYGTFN RAMLR LIPSLRTYAEP LTAAMVEFYTMS  
QERFTQDTQPHYIYSPREMTRWVRGIFEALRPLETLPVEGLIRIWAHEALRLFQDR LVED  
EERRWTDENIDTVALKHFPNIDREKAMSRPILYSNWLSKDYIPVDQEELRDYVKARLKVF  
YEEELDVPLVLFNEVL DHVLRIDRIFRQPQGHLLIGVSGAGKTTL SRFVAMNGLSVYQ  
IKVHRKYTGEDFDEDLRTVLR RSGCKNEKIAFIMDESNVLD SGFLERMNTLLANGEVPG  
LFEGDEYATLMTQCKEGAQKEGLMLDSHEELYKWFTS QVIRNLHVFTMNPSSSEGLKD

RAATSPALFNRCVLNWFGDWSTEALYQVGKEFTSKMDLEKPNYIVPDYMPVVYDKLPQ  
 PPSHREAIVNSCVFVHQTLHQANARLAKRGGRTMAITPRHYLDFINHYANLFHEKRSEL  
 EEQQMHLNVGLRRIKETVDQVEELRRDLRIKSQELEVKNAAANDKLKKMVKDQQEAEK  
 KKVMSQEIQEQLHKQEQEVIADKQMSVKEDLDKVEPAVIEAQNAVKSIIKKQHLVEVRSM  
 NPPAAVKLALESICLLLGESTTDWKQIRSIIMRENFIPTIVNFSAAEISDAIREKMKKNYMS  
 NPSYNYEIVNRASLACGPMVKWAIQNLNYADMLKRVEPLRNELQKLEDDAKDNQQKAN  
 EVEQMIRDLEASIARYKEEYAVLISEAQAIKADLAHAVEAKVNRSTALLKSLSAERERWEK  
 TSETFKNQMSTIAGDCLLSAAFIAYAGYFDQQMRQNLFTTWSHHLQQANIQFRTDIART  
 EYLSNADERLRWQASSLPADDLCTENAIMLKRFRNRYPLIIDPSGQATEFIMNEYKDRKIT  
 RTSFLDDAFRKNLESALRFGNPLLVDVESYDPVLNPVLNREVRRTGGRVLITLGDQDI  
 DLSPSFVIFLSTRDPTVEFPPDLCSRVTFVNFTVTRSSLQSQCLNEVLKAERPVDVDEKRS  
 DLLKLQGEFQLRLRQLEKSLLQALNEVKGRILDDDTIITLENLKREAAEVTRKVEETDIV  
 MQEVETVSQQYLPLSTACSSYFTMESLKQIHFLYQYSLQFFLDIYHNVLYENPNLKGVT  
 DHTQRLSIITKDLFQVAFNRVARGMLHQDHITFAMLLARIKLGTVGEPTYDAEFQHFLR  
 GNEIVLSAGSTPRIQGLTVEQAEAVVRLSCLPAFKDLIAKVQADEQFGIWLDSSSPEQTV  
 PYLWSEETPATPIGQAIHRLLLIQAFRPDRLLAMAHMFVSTNLGESFMSIMEQPLDLTHIV  
 GTEVKPNTPVLMCSVPGYDASGHVEDLAAEQNTQITSIAIGSAEGFNQADKAINAVKS  
 GRWVMLKNVHLAPGWLMLQLEKKLHSLQPHACFRLFLTMEINPKVPVNLRLRAGRIFVFEP  
 PPGVKANMLRTFSSIPVSRICKSPNERARLYFLLAWFHAIQERLRYAPLGWSKKYEFGE  
 SDLRSACDTVDTWLDDTAKASGRQNISPDKIPWSALKTLMAQSIYGGRVDNEFDQRLL  
 NTFLERLFTTRSFDSEFKLACKVDGHKDIQMPDGIRREEFVQWVELLPDTQTPSWLGLP  
 NNAERVLLTTQGVDMISKMLKMQMLEDDEDDLAYAETEEKTRTDSTSDGRPAWMRTLH  
 TTASNWLHLIPQTLSHLKRTVENIKDPLFRFFEREVKMGAKLLQDVRQDLADVQVCEG  
 KKKQTNYLRTLINELVKGILPRSWSHYTVPAGMTVIQWVSDFSERIKQLQNISLAAASGG  
 AKELKNIHVCLGGLFVPEAYITATRQYVAQANSWSLEELCLEVNVTTSSQGATLDACSFG  
 VTGLKLQGATCNNNKLSSLSNAISTALPLTQLRWVKQTNTEKKASVVTLPVYLNFTRADLI  
 FTVDFEATKEDPRSFYERGVAVLCTE

SEQ ID No:69

MMENHVSQASVTIRIADKEVTIKVPAGTRLLSQPCASDRFIQTLSHKQLQAEMMQSHMV  
 KDICLIGGKGCGKTVIAKNFADTLGYNIEPIMLYQDMTARDLLQQRYTLPNGDTAWRSSP  
 LVNAALEGKLVLLDGIHRVNAGTLAVLQRLIHDRELSLYDGSRLREDRYMRLKEELQLS  
 DEQLQKRSIFPIHPSFRIIALAEPPIVIGSTAHQWLGPFLTMFFFHYMKPLVKSEEIQVIKE  
 KVPNPQEALDKLLSFTHKLRETQDPTAQSLAASLSTRQLLRISRRLSQYPNENLHSAVT

KACLSRFLPSLARSALKNLADATIEINTDDNLEPELKDYKCEVTSGTLRIGAVSAPIYNA  
HEKMKVPDVLFDYDNIQHVVIMEDMLKDFLLGEHLLLVGNNQGVGKNKIVDRFLHLLNRPR  
EYIQLHRDTTVQTLTLQPSVKDGLIVYEDSPLVKAVKLGHILVVDEADKAPTNVTCILKTL  
VENGEMILADGRRIVANSANVNGRENVVVIHPDFRMIVLANRPGFPFLGNDFFGTLGDIF  
SCHAVDNPKPHSELEMLRQYGPVPEPILQKLVAAFGELRSLADQGIINYPYSTREVVNI  
VKHLQKFPTGLSSVVRNVFDFDSYNNDMREILINTLHKYGIPIGAKPTSVQLAKELTLPE  
QTFMGYWTIGQARSGMQKLLCPVETHHIDIKGPALINIQEYPIERHEERSLNFTEECASW  
RIPLDEINIICDIATSHENEQNTLYVVTCPNPASLYFMNMTGKSGFFVDFDIFPRTANGVW  
HPFVTVAPLGSPKGGQVVLHEQQSNVILLDDTTGRALHRLILPSEKFTSKKPFWWNKEE  
AETYKMCKEFSHKNWLVFYKEKGNLSLTVLDVLEGRTHHTISLPINLKTVFLVAEDKWLLVE  
SKTNQKYLLTKPAHIESEGSGVCQLYVLKEEPPSTGFGVTQETEFSSIPHKISSDQLSSEH  
LSSAVEQKIASPNRILSDEKNYATIVVGFPDLMSPSEVYSWKRPSSLHKRSGTDTSFYR  
GKKKRGTPKQSNCVTLTLDNQQVVRILPPGEVPLKDIYPKDVTPPQTSGYIEVTDLQSKKL  
RYIPIRSESLSPYTTWLSTISDTDALLAEWDKSGVVTVDMGGHIRLWETGLERLQSRSL  
MEWRNMIGQDDRNMQITINRDSGEDVSSPKHGKEDPDNMPHVGGNTWAGGTGGRDT  
AGLGGKGGPYRLDAGHTVYQVSQAEDAVPEEVKRAAREMGQRAFQQRLKEIQMSEY  
DAATYERFSGAVRRQVHSLRIILDNLQAKGKERQWLRHQATGELDDAKIIDGLTGEKAIY  
KRRGELEPQLGSPQQKPKRLRLVVDVSGSMYRFNRMDGRLERTMEAVCMVMEAFEN  
YEEKFYDIVGHSGDGYNIGLVPMNKIPKDNKQRLEILKTMHAHSQFCMSGDHTLEGTE  
HAIKEIVKEEADEYFVIVLSDANLSRYGIHPAKFAQILTRDPQVNAFAIFIGSLGDQATRLQ  
RTLPAGRSFVAMDTKDIPQILQQIFTSTMLSSV

SEQ ID No:70

MLERKYGGRLVTRHAARTIQTAFRQYQMKNKFERLRSSMSSENRMSSRRIVLSNMRMQF  
SFEGPEKVHSSYFEGKQVSVTNDGSQLGALVSPECGLSEPTTLKSPAPSSDFADAITE  
LEDAFSRQVKSLAESIDDALNCRSLHTEEAPALDAARARDTEPQTALHGMDHRKLD  
TASYSDVTLYIDEEELSPPLPLSQAGDRPSSTESDLRLRAGGAAPDYWALAHKEDKADT  
DTSCRSTPSLERQEQLRVEHLPLLTIEPPSDSSVDLSDRSERGSLKRQSAYERSLGG  
QQGSPKHGPHSGAPKSLPREPELRPRPPRPLDSHLAINGSANRQSKSESDYSDGDN  
DSINSTSNSNDTINCSSSESSSRDSLREQTLQTYHKEARNSWDSPAFSNDVIRKRHYR  
IGLNLFNKKPEKGVQYLIERGFPDTPVGVAFHLLQRKGLSRQMIGEFLGNRQKQFNDR  
VLDCVVDDEMDFSTMEALRKFQAHIRVQGEAQKVERLIEAFSQRYSICNPGVVRQFR  
NPDTIFILAFIILLNTDMYSPNVKPERKMKLEDFIKNLRGVDDGEDIPREMLMGIYERIRK  
RELKTNEHDHVSQVQKVEKLIVGKKPIGSLHPGLGCVLSLPHRRLVCYCRLFVDPDPNPK

QKLGLHQREIFLNDLLVTKIFQKKKNSVTYSFRQSFSLYGMQVLLFENQYYPNGIRLT  
SSVPGADIKVLINFNAPNPQDRKKFTDDLRESIAEVQEMEKHRIESELEKQKGVVRPSM  
SQCSSLKKESGNGTLSRACLDDSYASGEGLKRSALSSSLRDLSEAGKRGRRSSAGSLE  
SNVEFQPFEPQLQPSVLC

SEQ ID No:71

MPLKHYLLLLVGCQAWGAGLAYHGCPSECTCSRASQVECTGARIVAVPTPLPWNAMS  
LQILNTHITELNESPFNLISALIALRIEKNELSRITPGAFRNLGSLRYLSLANNKLQVLPIGLF  
QGLDSLESLLLSSNQLLQIQPAHFSQCSNLKELQLHGNHLEYIPDGAFDHLVGLTKLNLG  
KNSLTHISPRVFQHLGNLQVLRLYENRLTDIPMGTFDGLVNLQELALQQNQIGLLSPGLF  
HNNHNLQRLYLSNNHISQLPPSIFMQLPQLNRLTLFGNSLKELSLGIFGMPMPNLRELWLY  
DNHISSLPDNVFSNLRQLQVLILSRNQISFISPGAFNGLTELRELSLHTNALQDLGDNVFR  
MLANLQNISLQNNRLRQLPGNIFANVNGLMAIQLQNNQLENLPLGIFDHLGKLCERLYD  
NPWRCDSDILPLRNWLLNQPRLGTDTPVPCFSPANVRGQSLIINNVNAVPSVHVPEVP  
SYPETPWYPDTPSYPDTTSVSSTTELTSPVEDYTDLTTIQVTD DRSVWGMTHAHSGLAI  
AAIVIGIVALACSLAACVGCCCCCKKRSQAVLMQMKAPNEC

SEQ ID No:72

MRGSHRAAPALRPRGRLWPVLAVLAAAAAAGCAQAAMDECTDEGGRPQRCMPEFVN  
AAFNVTVVATNTCGTPPEEYCVQGTGVTGVTKSCHLCDAGQPHLQHGAFLTDYNNQA  
DTTWWQSQTMLAGVQYPSSINLT LHLGKAFDITYVRLKFHTSRPESFAIYKRTREDGPW  
IPYQYYSGSCENTYSKANRGFIRTGGDEQQALCTDEFSDFSPLTGGNVAFASTLEGRPS  
AYNFDNSPVLQEWVTATDIRVTNLRLNTFGDEVFNDPKVLKSYYYAISDFAVGGRCKCN  
GHASECMKNEFDKLV CNCKHNTYGVDCCKLPFFNDRPWRRATAESASECLPCDCNG  
RSQECYFDPELYRSTGHGGHCTNCQDNTDGAHCERCENFFRLGNNEACSSSCHCSP  
VGSLSLSTQCDSYGRCSCKPGVMGDKCDRCQPGFHSLTEAGCRPCSCDPSGSDCECNV  
ETGRCVCKDNVEGFNCERCKPGFFNLESSNPRGCTPCFCFGHSSVCTNAVGYSVYSIS  
STFQIDEDGWRAEQRDGSEASLEWSSERQDIAVISDSYFPRYFIAPAKFLGKQVLSYGQ  
NLSFSFRVDRRDTRLAEDLVLEGAGLRVSVPLIAQGN SYPSETTVKYVFR LHEATDYP  
WRPALTPFEFQKLLNNLTSIKIRGTYSERSAGYLDDVTLASARPGPGVPATWVESCTCP  
VGYGGQFCMCLSGYRRETPNLGPYSPCVLCACNGHSETCDPETGVCNCRDNTAGP  
HCEKCS DGYGDSTAGTSSDCQPCPCPGGSSCAVVPKTKEVVCTNCPTGTTGKRCEL  
CDDGYFGDPLGRNGPVRLCRLCQCSDNIDPNAVGN CNRLTGECLKCIYNTAGFYCDR  
CKDGGFFGNPLAPNPADKCKACNCNPNYGTMTKQQSSCNPVTGQCECLPHVTGQDCGAC

DPGFYNLQSGQGCERCDCALGSTNGQCDIRTGQCECQPGITGQHCCERCEVNHFGF  
 GPEGCKPCDCHPEGSLSLQCKDDGRCECREGFVGNRCDQCEENYFYNRSWPGCQE  
 CPACYRLVKDKVADHRVKLQELES LIANLGTGDEMVTDQAFEDRLKEAEREVMDLLRE  
 AQDVKDVDQNLMDRLQRVNNTLSSQISRLQNIRNTIEETGNLAEQARAHVENTERLIEIA  
 SRELEKAKVAAANVSVTQPESTGDPNNMTLLAEEARKLAERHKQEADDIVRVAKTAND  
 TSTEAYNLLLRTLAGE NQTAFEIEELNRKYEQAKNISQDLEKQAARVHEEAKRAGDKAV  
 EIYASVAQLSPLDSETLENEANNIKMEAENLEQLIDQKLKDYEDLREDMRGKELEVKNLL  
 EKGKTEQQTADQLLARADAAKALAEAAKKGRDTLQEANDILNNLKDFDRRVNDNKTA  
 AEEALRKIPAINQTITEANEKTREAAQALGSAAADATEAKNKAHEAERIASAVQKNATST  
 KAEAERTFAEVTDL DNEVNNMLKQLQEAEKELKRKQDDADQDMMMAGMASQAAQEA  
 EINARKAKNSVTSLLSIINDLLEQLGQLD TVDLNKLNEIEGTLNKAKDEMKVSDLRKVSD  
 LENEAKKQEA AIMDYNRDIEEIMKDIRNLEDIRKTLPSGCFNTPSIEKP

## SEQ ID No:73

MAAATEHNRPSGDRNLERRCSPNLSREVL YEIFRSLHTLVGQLDLRDDVVKITIDWNK  
 LQSLSAFQPALLFSALEQHILYLQPF LAKLQSPIKEENTTAVEEIGRTEMGNKNEVNDKF  
 SIGDLQEEEEKHKESDLRDVKKTIHFDP EVVQIKAGKAEIDRRISAFIERKQAEINENNVR  
 EFCNVIDCNQENSCARTDAIFTPYPGFKSHVKVSRVVNTYGPQTRPEGIPGSGHKPNS  
 MLRDCGNQAVEERLQNI EHLRLQTGGPVPRDIYQRIKKLEDKILELEGISPEYFQSVSF  
 SGKRRKVQPPQQNYSLAE LDEKISALKQALLRKSREAESMATHHLP

## SEQ ID No:74

LCNGVND CGDNSDESPQQNCRPRTGEENCNVNNGGCAQKCQMVRGAVQCTCHTG Y  
 RLTEDGHTCQDVNECAEEGYCSQGCTNSEGAFQCWCETGYELRPDRRSCKALGPEP  
 VLLFANRIDIRQVLPHRSEY TLLLNNLENAIALDFHHRREL VFWSDVTLD RILRANLNGSN  
 VEEVVSTGLESPGGLAVDWVHDKLYWTD SGTSRIEVANLDGAHRKVLLWQNLEKPRAI  
 ALHPMEGTIYWTDWGNTPRIEASSMDGSGRRRIADTHLFWPNGLTIDYAGRRMYWVDA  
 KHHVIERANLDGSHRKAVISQGLPHPF AITVFEDSLYWTDWHTKSINSANKFTGKNQEII  
 RNKLHFPMDIHTLHPQRQPAGKNRCGDNNGGCTHLCLPSGQNYTCACPTGFRKISSH  
 ACAQSLDKFLLFARRMDIRRISFDTE DLSDDVIPLADVRS AVALDWDSRDDHVYWTDVS  
 TDTISRAKWDGTGQEVVVDTSLESPAGLAIDWVTNKLYWTDAGTDRIEVANTDGS MRT  
 VLIWENLDRPRDIVVEPMGGYMYWTDWGASPKIERAGMDASGRQVISSNLTPNGLA  
 IDYGSQRLYWADAGMKTIEFAGLDGSKRKVLIGSQLPHPFGLTLYGERIYWTDWQTKSI  
 QSADRLTGLDRET LQENLENLMDIHVFHRRRPPVSTPCAMENGGC SHLCLRSPNPSGF

SCTCPTGINLLSDGKTCSPGMNSFLIFARRIDIRMVSLDIPYFADVVPINITMKNTIAVGV  
 DPQEGKVYWSDESTLHRISRANLDGSQHEDIITTGLQTTDGLAVDAIGRKVYWTDGTNR  
 IEVGNLDGSMRKVLVWQNLDSRAIVLYHEMGFMYWTDWGENAKLERSGMDGSDRA  
 VLINNNLGWPNGLTVDKASSQLLWADAHTERIEAADLNGANRHTLVSPVQHPYGLTLLD  
 SYIYWTDWQTRSIRADKGTGSNVILVRSNLPGLMDMQAVDRAQPLGFNKCGRNGG  
 CSHLCLPRPSGFSCACPTGIQLKGDGKTCDPSPETYLLFSSRGSIRRISLDTSDHTDVHV  
 PVPELNNVISLDYDSVDGKVYYTDVFLDVIRRADLNGSNMETVIGRGLKTTDGLAVDWV  
 ARNLYWTDGTGRNTIEASRLDGSCRKVLINNSLDEPRAIAVFPRKGYLFWTDWGHIAKIER  
 ANLDGSEKVLINTDLGWPNGLTLDYDTRRIYWVDAHLDRIESADLNGKLRQVLVGHVS  
 HPFALTQQDRWIYWTDWQTKSIQRVDKYSGRNKETVLANVEGLMDIIVSPQRQTGTN  
 ACGVNNGGCTHLCFARASDFVCACPDEPDSQPCSLVPGLVPPAPRATGMSEKSPVLP  
 NTPPTTLYSSTTRTRTSLEEVEGRCSEARLGLCARSNDAPPAAPGEGLHISYAIGGL  
 LSILLILVVIAALMLYRHKKSFTDPGMGNLTYSNPSYRTSTQEVKIEAIPKPAMYNLQCY  
 KKEGGPDHNYTKEKIKIVEGICLLSGDDAEWDDLKQLRSSRGGLLRDHVCMKTDTVSIQ  
 ASSGSLDDTEMEQLLQEEQSECSSVHTAATPERRGSLPDTGWKHERKLSSSESQV

SEQ ID No:75

MAPIGLKAVVGEKIMHDDVIKKVKKKGWVKLVVDQLSMRMLSSCCKMTDIMTEGITIVED  
 INKRREPLPSLEAVYLITPSEKSVHSLISDFKDPPTAKYRAAHVFFTDSCPDALFNELVKS  
 RAAKVIKTLTEINIAFLPYESQVYSLDSADSFQSFYSPHKAQMKNPILERLAEQIATLCATL  
 KEYPAVRYRGEYKDNALLAQLIQDKLDAYKADDPTMGEGPDKARSQLLILDRGFDPSSP  
 VLHELTFQAMSVDLLPIENDVYKYETSGIGEARVKEVLLDEDDDLWIALRHKHIAEVSQE  
 VTRSLKDFSSSKRMNTGEKTTMRDLSQMLKKMPQYQKELSKYSTHLHLAEDCMKHYYQ  
 GTVDKLCRVEQDLAMGTDAEGEIKIDPMRAIVPILLDANVSTYDKIRIILLYIFLKNGITEE  
 NLNKLQHAQIPPEDSEIITNMAHLGVPIVTDSTLRRRSKPERKERISEQTYQLSRWTPIIK  
 DIMEDTIEDKLDTKHYPYISTRSSASFSTTAVSARYGHWKHNKAPGEYRSGPRLIIFILGG  
 VSLNEMRCAYEVTQANGKWEVLIGSTHILTPTKFLMDLRHPDFRESSRVSFEDQAPTM  
 E

SEQ ID No:76

MSVKEAGSSGRREQAAYHLHIYPQLSTTESQASCRVTATKDSTTSVVIKDAIASLRLDG  
 TKCYVLVEVKESGGEEWVLDANDSPVHRVLLWPRRAQDEHPQEDGYFFLLQERNADG  
 TIKYVHMQLVAAQATATRRRLVERGLLPRQQADFDDLCNLPELTEGNLLKNLKHRFLQQKI  
 YTYAGSILVAINPFKFLPIYNPKYVKMYENQQLGKLEPHVFALADVAYYTMLRKRVNQCI

VYPGESGSGKTQSTNFLIHCLTALSQKGYASGVERTILGACPVLEAFGNAKTAHNNNSS  
RFGKFIQVSYLESIGVIRGAVVEKYLLEKSRLVSQEKDERNYHVFYLLLGVSEEERQEF  
QLKQPEDYFYLNQHNLIKIEDGEDLKHDFERLKQAMEMVGFLPATKKQIFAVLSAILYLGN  
VTYKKRATGREEGLEVGPPEVLDTLSQLLKVKREILVEVLTKRKTVTVNDKLILPYSLSEA  
ITARDSMAKSLYSALFDWIVLRINHALLNKKDVEEAVSCLSIGVLDIFGFEDFERNSEFQF  
CINYANEQLQYYFNQHIFKLEQEEYQGEGITWHNIGYTDNVGCIHLISKKPTGLFYLLDEE  
SNFPHATSQTLLAKFKQQHEDNKYFLGTPVMEPAFIIQHFAGKVKYQIKDFREKNMDYM  
RPDIVALLRGSDSSYVRELIGMDPVAVFRWAVLRAAIRAMAVLREAGRLRAERAEGAAG  
MSSPGAQSHPEELPRGASTPSEKLYRDLHNQMIKSIKGLPWQGEDPRSLLSRLQK  
PRAFILKSKGIKQKQIIPKNLLDSKSLKLIISMTLHDRTTKSLLHLHKKKKPPSISAQFQTS  
NKLLEALGKAEPFFIRCIRSNAEKKELCFDDELVLQQLRYTGMLETVRIRRRSGYSAKYTF  
QDFTEQFQVLLPKDAQPCREVISTLLEKMKIDKRNYQIGKTKVFLKETERQALQETLHRE  
VVRKILLQSWFRMVLERRHFLQMKRAAVTIQACWRSYRVRRALERTQAAVYLQAAWR  
GYWQRKLYRHQKQSIIRLQSLCRGHLQRKSFSQMISEKQKAEEKEREALAAAGAE  
GGQQAAGGQVAEQGPEPAEDGGHLASEPEVQPSDRSPLEHSSPEKEAPSPEKTL  
PPQKTVAESHEKVPSSREKRESRRQRGLEHVKFQNKHIQSCKEESALREPSRRVTQE  
QGVSLLEDKKESREDETLLVETEAEANTSQKQPTEQPQAMAVGKVSEETEKTLPSGSP  
RPGQLERPTSLALDSRVSPAPGSAPETPEDKSKPCGSPRVQEKPDSPGGSTQIQRYL  
DAERLASAVELWRGKKLVAAASPSAMLSQSLDLSDRHRATGAALTPTEERRTSFSTSD  
VSKLLPSLAKAQPAEETDGERSAKKPAVQKKKPGDASSLPDAGLSPGSQVDSKSTFK  
RLFLHKTOKDKYSLEGAEELNAVSGHVLEATTMKGLEAPSGQQRHAAGEKRTKE  
PGGKGKKNRNVKIGKITVSEKWRESVFRQITNANELKYLDEFLLNKINDLRSQKTPIESLF  
IEATEKFRSNIKTMYSVPNGKIHVGYKDLMENYQIVVSNLATERGQKDTNLVLNLFQSLL  
DEFTRGYTKNDFEPVKQSKAQKKRKQERAVQEHNHGFASYQVSIPQSCEQCLSYIW  
LMDKALLCSVCKMTCHKKCVHKIQSHCSYTYGRKGEPGAEPGHFGVCVDSLTSKASV  
PIVLEKLEHVEMHGLYTEGLYRKSGAANRTRELQALQTDPAAVKLENFPIHAITGVLK  
QWLRELPEPLMTFAQYGDFLRAVELPEKQEQLAAIYAVLEHLPEANHNSLERLIFHLVKV  
ALLEDVNRMSPGALAIIFAPCLLRCPDNDPLTSMKDVLKITTCEMLIKEQMRKYVKM  
EEISQLEAAESIAFRRLSLLRQANANKSPKTREPAGGAGRLLTTSRVSPSPSTRNLALGS  
WRSALRTRGTGRPARPGRARALRRRPPRPARESPAQPPRSRPRVRTETPSPLSSGP  
PPSRSTNGMAPLRR

SEQ ID No:77

MAPRLCSISVTARRLLGGPGPRAGDVASAAAARFYSKDNEGSWFRSLFVHKVDPRKDA  
 HSTLLSKKETSPLYKIQFHNVKPEYLDAYNSLTEAVLPKLHLDEDYPCSLVGNWNTWYG  
 EQDQAVHLWRFSGGYPALMDCMNKLKNNKEYLEFRRERSQMLLSRRNQLLLEFSFWN  
 EPQPRMGPNIELRTYKLKPGTMIEWGNNWARAIKYRQENQEAVGGFFSQIGELYVVH  
 HLWAYKDLQSREETRANAARWRKRGWDENVYYTVPLVRHMESRIMIPLKISPLQ

SEQ ID No:78

MAARVLRARGAAWAGGLLQRAAPCSLLPRLRTWTSSSNRSREDSWLKSLFVRKVDPR  
 KDAHSNLLAKKETSPLYKLQFHNVKPECLEAYNKICQEVLPKIHEDKHYPCTLVGTWNT  
 WYGEQDQAVHLWRYEGGYPALTEVMNKLRENKEFLEFRKARSDMLLSRKNQLLLEFS  
 FWNEPVPKSGPNIELRSYQLRPGTMIEWGNYWARAIRFRQDNEAVGGFFSQIGQLY  
 MVHHLWAYRDLQTREDIRNAAWHKHGWEEELVYYTVPLIQEMESRIMIPLKTSPLQ

SEQ ID No:79

MGTALLQRGGCFLCLSLLLLCWAELGSGLEFPGAEGQWTRFPKWNACCESSEMSFQ  
 LKTRSARGLVLYFDDEGFCDLFELILTRGGRLQLSFSIFCAEPATLLADTPVNDGAWHSV  
 RIRRQFRNTTLFIDQVEAKWVEVKSKRRDMTVFSGLFVGGLPPELRAAALKTLASVRE  
 REPFGKWIRDVRVNSSQVLPVDSGEVKLDDEPPNSGGGSPCEAGEEGEGGVCLNGG  
 VCSVDDQAVCDCSRTGFRGKDCSQEDNNVEGLAHLMMGDQGKSKGKEEYIATFKG  
 SEYFCYDLSQNPIQSSSDEITLSFKTLQRNGLMLHTGKSADYVNLALKNGAVSLVINLGS  
 GAFEALVEPVNGKFNDNAWHDKVTRNLRQHSGIGHAMVTISVDGILTTTGYTQEDYT  
 MLGSDDFFYVGGSPSTADLPGPSVSNFMGCLKEVVYKNNDVRLELSRLAKQGDPKM  
 KIHGWVAFKENVATLDPITFETPESFISLPKWNNAKKTGSISFDFRTTEPNGLILFSHGKP  
 RHQKDAKHPQMIKVDFFAIEMLDGHLYLLLDMSGTIIKIKALLKKVNDGEWYHVDQFQD  
 GRSQTISVNTLRTPYTAPGESEILDLDDELYLGGLPENKAGLVFPTEVWTALLNYGYVG  
 CIRDLFIDGQSKDIRQMAEVQSTAGVKPSCSKETAKPCLSNPCKNNGMCRDGNRYV  
 CDCSGTGYLGRSCEREATVLSYDGSMFMKIQLPVVMHTEAEDVSLRFRSQRAYGILMA  
 TTSRDSADTLRLELDAGRVKLTVNLDICIRINCNSKGPETLFAGYNLNDNEWHTVRVVR  
 RGKSLKLTVDQDQAMTGQMGADHTRLEFHNIETGIITERRYLSVSPSNFIGHLQSLTFN  
 GMAYIDLCKNGDIDYCELNARFGFRNIIADPVTFTKSSYVALATLQAYTSMHLFFQFKT  
 TSLDGLILYNSGDGNDFIVVELVKGYLHYVFDLGNGANLIKSSNKPLNDNQWHNVMIS  
 RDTSNLHTVKIDTKITTQITAGARNLDLKSPLYIGGVAKETYKSLPKLVHAKEGFQGCCLAS  
 VDLNGLRPDLISDALFCNGQIERGCEGPSTTCQEDSCSNQGVCLQQWDGFSDCDSMT  
 SFSGPLCNDPGTTYIFSGGGGQITYKWPPNDRPSTRADRLAIGFSTVQKEAVLVRVDSS

SGLGDYLELHIHQGKIGVKFNVGTDDIAIEESNAIINDGKYHVVRFTRSGGNATLQVDSW  
 PVIERYPAGRQLTIFNSQATIIIGGKEQGQPFQGGQLSGLYYNGLKVLNMAAENDANIAIVG  
 NVRLVGEVPSSMTTESTATAMQSEMSTSIMETTTTLATSTARRGKPPTKEPISQTTDDIL  
 VASAECPSSDDEDIDPCEPSSGGLANPTRAGGREPYPGSAEVIRESSSTTGMVVGIVAAA  
 ALCILILLYAMYKYRNRDEGSYHVDESRNYISNSAQSNAGAVVKEKQPSSAKSSNKNKNKN  
 KDKEYYYV

SEQ ID No:80

MTTQQIDLQGGPGPWGFRLVGGKDFEQPLAISRVTPGSKAALANLCIGDVITAIDGENTS  
 NMTHLEAQNRIGCTDNLTLTVARSEHKVWSPLVTEEGKRHPYKMNLASEPQEVHLIG  
 SAHNRSAMPFTASPASSTTARVITNQYNNPAGLYSSENISNFNNALESKTAASGVEANS  
 RPLDHAQPPSSLVIDKESEVYKMLQEKKQELNEPPKQSTSFLVLQEILESEEKGDPNKPS  
 GFRSVKAPVTKVAASIGNAQKLPMCDKCGTGIVGVFVKLRDRHRHPECYVCTDCGTNL  
 KQKGHFFVEDQIYCEKHARERVTPPEGYEVVTVFPK

SEQ ID No:81

MTSAAPAKKPYRKAPPEHRELRLLEIPGSRLEQEEPLTDAERMKLLQEENEELRRRLASA  
 TRRTEALERELEIGQDCLELELGQSREELDKFKDKFRRLQNSYTASQRTNQELEDKLT  
 LIKKAEMDRKTLTLDWEIVELTNKLLDAKNTINKLEELNERYRLDCNPAVQLLKCNKSHFRN  
 HKFADLPCELQDMVRKHLHSGQEAAASPGPAPSLAPGAVVPTSVIARVLEKPESLLLNSA  
 QSGSAGRPLAEDVFVHVDMSSEGVPGBPAPSPAPGSPTPQPNGECHSLGTARGSPEEE  
 LPLPAFEKLNYPYPTSPPHPLYPGRRVIEFSEDKVRIPRNSPLPNECTYATRQAISLSLVEE  
 GSERARPSVPSTPASAQASPHHQPSAPLTLAPASSASSEEDLLVSWQRAFDVDRTP  
 PPAAVAQRTAFGRDALPELQRHFAHSPADRDEVVQAPSARPEESELLLPTEPDSGFPR  
 EEEELNLPISPEEERQSLLPINRGTEEGPGTSHTEGRAWPLPSSSRPQRSPKRMGVHH  
 LHRKDSLTAQAEQGNLLN

SEQ ID No:82

MGTTASTAQQTVSAGTPFEGLQGSGTMDSRHSVSIHSFQSTSLHNSKAKSIIPNKVAPV  
 VITYNCKEEFQIHDELLKAHYTLGRLSDNTPEHYLVQGRYFLVRDVTEKMDVLGTVGSC  
 GAPNFRQVQGGLTVFGMGQPSLSGFRRVLQKLQKDGHRECVIFCVREEPVLFLRADE  
 DFVSYTPRDKQNLHENLQGLGPGVRVESLELAIRKEIHDFQAQLSENTYHVYHNTEDLWG  
 EPHAVAIHGEDDLHVTEEVYKRPLFLQPTYRYHRLPLPEQGSPLAQDLAFVSVLRETP  
 SLLQLRDAHGPPPALVFSCQMGVGRTNLGMVLGTLILLHRSGTTSQPEAAPTQAKPLP

MEQFQVIQSFLRMVPQGRRMVEEVDRAITACAELHDLKEVVLENQKKLEGIRPESPAQ  
 GSGSRHSVWQRALWSLERYFYLLFNYYLHEQYPLAFALSFSRWLCAHPELYRLPVTLS  
 SAGPVAPRDLIARGSLREDDLVSPDALSTVREMDVANFRRVPRMPIYGTAQPSAKALG  
 SILAYLTDARRLRKVVWVSLREEAVLECDGHTYSLRWPGPPVAPDQLETLEAQLKAHL  
 SEPPPGKEGPLTYRFQTCLTMQEVFSQHRRACPGITYHRIPMPDFCAPREEDFDQELLE  
 ALRAALSKDPGTGFVFSCLSGQGRTTAMVVAVLAFWHIQGFPEVGEEELVSVPAKF  
 TKGEFQVVMKVQLLPDGHRVKKEVDAALDTVSETMTMPMHYHLREIICTYRQAKAAKE  
 AQEMRRLQLRSLQYLERYVCLILFNAYLHLEKADSWQRPFSTWMQEVASKAGIYEILNE  
 LGFPELESGEDQPFSLRYRWQEQSCSLEPSAPEDLL

SEQ ID No:83

MEALPLLAATTPDHGRHRRLLLLPLLLFLLPAGAVQGWETEERPRTREEECHFYAGGQ  
 VYPGEASRVSVADHSLHLSKAKISKAPYWEGTAVIDGEFKELKLTDIRGKYLVEFFYPL  
 DFTFVCPTEIIAFGDRLEEFRSINTEVVACSVDSQFTHLAWINTPRRQGGGLPIRIPLLSD  
 LTHQISKDYGIVYLED SGHTLRGLFIIDDKGILRQITLNDLPVGRSVDETLRLVQAFQYTDK  
 HGEVCPAGWKPGSETIIPDPAGKLKYFDKLN

SEQ ID No:84

MAALYRPGRLRNWHGLSPLGWPSCRSIQTLRVLSGDLGQLPTGIRDFVEHSARLCQPE  
 GIHICDGTEAENTATLTLEQQGLIRKLPKYNNCWLARTDPKDVARVESKTVIVTPSQRD  
 TVPLPPGGARGQLGNWMSPADFQRAVDERFPGCMQGRTMYVLPFSMGPVGSPLSRI  
 GVQLTDSAYVVASMRIMTRLGTPVLQALGDGDFVKCLHSGVQPLTGQGEVPSQWPCN  
 PEKTLIGHVPDQREIISFGSGYGGNSLLGKKCFALRIASRLARDEGWLAEHMLILGITSPA  
 GKKALCAAFFPSACGKTNLAMMRPALPGWKVECVGDDIAWMRFDSEGRRLRAINPENG  
 FFGVAPGTSATTNPAMATIQSNTIFTNVAETSDGGVYWEGIDQPLPPGVTVTSWLKGP  
 WKPGDKEPCAHPNSRFCAPARQCPIMDPAWEAPEGVPIDAIIFGGRRPKGVPVLYEAF  
 NWRHGVFVGRAMRSESTAAAEHKGIIMHDPFAMRPFFGYNFGHYLEHWLSMEGRKG  
 AQLPRIFHVNWFRRDEAGHFLWPGEFGENARVLDWICRRLEGEDSARETPIGLVPKEGA  
 LDLSGLRAIDTTQLFSLPKDFWEQEVDIRSYLTEQVNQDLPKEVLAELEALERRVHKM

SEQ ID No:85

MLPAATASLLGPLLTACALLPFAQQQTPNYTRPVFLCGGDVKGESGYVASEGFNP  
 PNKECIWTITVPEGQTVSLSFRVFDLELHPACRYDALEVFAGSGTSGQRLGRFCGTFRP  
 APLVAPGNQVTLRMTTDEGTGGRGFLLWYSGRATSGTEHQFCGGRLEKAQGTLTTPN

WPESDYPPGISCSWHIIAPPDQVIALTFEKFDLEPD TYCRYDSVSVFNGAVSDDSRRLG  
 KFCGDAVPGSISSEGNELLVQFVSDLSVTADGFSASYKTLPRGTAKEGQGPGPKRGTE  
 PKVKLPPKSQPPEKTEESPSAPDAPTCPKQCRRTGTLQSNFCASSLVVTATVKSMVRE  
 PGEGLAVTVSLIGAYKTGGLDLSPPTGASLKFYVPCKQCPPMKKGVSYLLMGQVEEN  
 RGPVLPPESFVVLHRPNQDQILTNLSKRKCPSQPVRAAASQD

SEQ ID No:86

MRMTMEEMKNEAETTSMVSMPLYAVMYPVFNELERNLSAAQTLRAAFIKA EKENPGL  
 TQDIIMKILEKKSVEVNFTESLLRMAADDVEEYMIERPEPEFQALNEKARALKQILSKIPD  
 EINDRVRF LQTIKDIASAIKELLDTVNNVFKKYQYQNRRALEHQKKEFVKYSKSFSDTLKT  
 YFKD GKAINVFVSANRLIHQTNLILQTFKTVA

SEQ ID No:87

MTSALTQGLERIPDQLGYLV LSEGAVLASSGDLENDEQAASAISELVSTACGFRLHRGM  
 NVPFKRLSGEPLPLPLVVVLGAGGYFQGLLG FSSSSLLPSPGVSGLATFLPLGLPGIRIV  
 NEKARERRSSRGHSSSNL

SEQ ID No:88

MLDSSDSSSQPHWSNELIAEQLQQQVSQLQDQLDAELEDKRKVLLELSREKAQNEDLK  
 LEVTN ILQKHKQEV ELLQNAATISQPPDRQSEPATHPAVLQENTQIEPSEPKNQEEKLS  
 QVLNELQVSHAETTLELEKTRDMLILQRKINVCYQEELEAMMTKADNDNRDHKEKLERL  
 TRLLDLKNNRIKQLEGILRSHDLPTSEQLKDVAYGTRPLSLCLETLP AHGDEDKVDISLLH  
 QGENLFELHIHQAF L TSAALAQAGDTQPTTFCTYSFYDFETHCTPLSVGPQPLYDFTSQ  
 YVMETDSLFLHYLQEASARLDIHQAMASEHSTLAAGWICFDRVLETVEKVHGLATLIGA  
 GGEEFGVLEYWMRLRFPIKPSLQACNKRKKAQVYLSTDVLGGRKAQEEEF RSESWE P  
 QNELWIEITKCCGLRSRWLGTQPSPYAVYRFFTFSDHDTAIPASNNPYFRDQARFPVLV  
 TSDLDHYLRREALSIHVFDDEDLEPGSYLGRARVPLLPLAKNESIKGDFNLTDPAEKPNG  
 SIQVQLDWKFPYIPPE SFLKPEAQTKGKDTKDSSKISSEEEKASFPSQDQMASPEVPIEA  
 GQYRSKRKPPHGGGERKEKEHQVVSYSRRKHGKRIGVQGKNRMEYLSLNILNGNTPQQ  
 VNYTEWK FSETNSFIGDGFKNQHEEEEMTL SHSALKQKEPLHPVNDKESSEQGSEVSE  
 AQTTDSDDVIVPPMSQKYPKADSEKMCIEIVSLAFYPEAEVMSDENIKQVYVEYKFYDLP  
 LSETETPVSLRKPRAGEEIH FHF SKVIDLDPQEQQGRRRFLFDMLNGQDPDQGH LKFTV  
 VSDPLDEEKKECEEVGYAYLQLWQILESGRDILEQELDIVSPEDLATPIGRLKVSLQAAA  
 VLHAIYKEMTEDLFS

SEQ ID No:89

MERSGWARQTFLLALLLGATLRARAAAGYYPRFSPFFFLCTHHGELEGDGEQGEVLISL  
HIAGNPTYVPGQEYHVTISTSTFFDGLLVTGLYTSTSVQASQSIGGSSAFGFGIMSDHQ  
FGNQFMCSVVASHVSHLPTTNLSFIWIAPPAGTGCVNFMATATHRGQVIFKDALAQQLC  
EQGAPTDVTVHPHLAEIHSDSIILRDDFDSYHQLQLNPNIWVECNCETGEQCGAIMHG  
NAVTFCEPYGPRELITTGLNTTTTASVLQFSIGSGSCRFSYSDPSIIVLYAKNNSADWIQLE  
KIRAPSNVSTIIHILYPEDAKGENVQFQWKQENLRVGEVYEACWALDNILIINSAHRQVV  
LEDSLDPVDTGNWLFFPGATVKHSCQSDGNSIYFHGNEGSEFNFATTRDVDLSTEDIQ  
EQWSEEFESQPTGWDVLGAVIGTECGTIESGLSMVFLKDGERKLCTPSMDTTGYGNLR  
FYFVMGGICDPGNSHENDIILYAKIEGRKEHITLDTLSYSSYKVPSLVSVVINPELQTPATK  
FCLRQKNHQGHNRNVWAVDFFHVLPLPSTMSHMIQFSINLGCCTHQPGENSVSLEFST  
NHGRSWSLLHTECLPEICAGPHLPHSTVYSSSENYSGWNRITIPNAALTRNTRIRWRQ  
TGPILGNMWAIDNVYIGPSCCLKFCSGRGQCTRHGCKCDPGFSGPACEMASQTFPMFIS  
ESFGSSRLSSYHNFYSIRGAEVSFSGCVLASGKALVFNKEGRRQLITSFLDSSQSRFLQ  
FTLRLGSKSVLSTCRAPDQPGEGVLLHYSYDNGITWKLLEHYSYLSYHEPRIISVELPGD  
AKQFGIQFRWWQPYHSSQREDVWAIDEIIMTSVLFNSISLDFTNLVEVTQSLGFYLGNV  
QPYCGHDWTLCFTGDSKLASSMRYVETQSMQIGASYMIQFSLVMGCGQKYTPHMDN  
QVKLEYSTNHGLTWHLVQEECLPSPSCQEFTSASIYHASEFTQWRRVIVLLPQKTWS  
SATRFRWSQSYYTAQDEWALDSIYIGQQCPNMCSGHSGCDHGICRCDQGYQGTECH  
PEAAPSTIMSDFENQNGWESDWQEVIGGEIVKPEQGCQGVISSGSSLYFSKAGKRQLV  
SWDLDTSWVDFVQFYIQIGGESASCNKPDSREEGVLLQYSNNGGIQWHLLAEMYFSDF  
SKPRFVYLELPAAAKTPCTRFRWWQPVFSGEDYDQWAVDDIILSEKQKQIIPVINPTLP  
QNFYEKPAFDYPMNQMSVWLMLANEGMVKNETFCAATPSAMIFGKSDGDRFAVTRDL  
TLKPGYVLQFKLNIGCANQFSSTAPVLLQYSHDAGMSWFLVKEGCYPASAGKGCEGNS  
RELSEPTMYHTGDFEEWTRITIVIPRSLASSKTRFRWQIQUSSSQKNVPPFGLDGVYISEP  
CPSYCSGHGDCISGVCFCDLGYTAAQGTCSVSNVPHNEMFDRFEGKLSPLWYKITGA  
QVGTGCGTLNDGKSLYFNGPGKREARTVPLDTRNIRLVQFYIQIGSKTSGITCIKPRTRN  
EGLIVQYSNDNGILWHLLRELDMSFLEPQIISIDLQDAKTPATAFRWWQPQHGHKHA  
QWALDDVLIGMNDSSQTGFQDKFDGSIDLQANWYRIQGGQVDIDCLSMMDTALIFTENIG  
KPRYAETWDFHVSASTFLQFEMSMGCSKPFSSNSHSVQLQYSLNNGKDWHLVTEECVP  
PTIGCLHYTESSYTSERFQNWKRITVYLPLSTISPRTFRFRWQIQUSSSQKNVPPFGLDGVYISEP  
ASGCPWMCSGRGICDAGRCVCDRGFGGPYCVPVVPLPSILKDDFNGLNHPDLWPEVY  
GAERGNLNGETIKSGTSLIFKGEGLRMLISRDLCTNTMYVQFSLRFIAKSTPERSHSILL

QFSISGGITWHLMDEFYFPQTTNILFINVPLPYTAQTNATRFRLWQPYNNGKKEEIWIVD  
DFIIDGNVNNPVMLLDTFDFGPREDNWFFYPGGNIGLYCPYSSKGAPEEDSAMVFVS  
NEVGEHSITTRDLNVNENTIIQFEINVGCSTDSSSADPVRLEFSRDFGATWHLLLPLCYH  
SSSHVSSLCSTEHHPSSSTYYAGTMQGWRRREVWHFGKLHLCGSVRFRWYQGFYPAGS  
QPVTWaidNVYIGPQCEEMCNGQGSCINGTKCICDPGYSGPTCKISTKNPDFLKDDFEG  
QLESDRFLLMSSGGKPSRKCGILSSGNNLFFNEDGLRMLMTRDLDLSHARFVQFFMRLG  
CGKGVPDPRSQPVLLQYSLNGLLSWSLLQEFLFSNSSNVGRYIALEIPLKARSGSTRLR  
WWQPSENGHFYSPWVIDQILIGGNISGNTVLEDDFTTLDsrKwLLHPGGTKMPVCGST  
GDALVFIEKASTRYVVDVAVNEDSFLQIDFAASCSVTDSYAIELEYSVDLGLSWHPL  
VRDCLPTNVECSRYHLQRILVSDTFNKWTRITLPLPPYTRSQATRFRWHQPAPFDKQQ  
TWaidNVYIGDGCIDMCSGHGRCIQGNCVCDEQWGGLYCDDPETSLLPTQLKDNFNRA  
PSSQNWLTVNGGKLSTVCGAVASGMALHFSGGCSRLLVTVDLNLTNAEFIQFYFMYGC  
LITPNNRNQGVLLYESVNGGITWNLLMEIFYDQYSKPGFVNILLPPDAKEIATRFRWWQP  
RHDGLDQNDWaidNVLISGSADQRTVMLDTFSSAPVPQHERSPADAGPVGRIAFDMFM  
EDKTSVNEHWLFDHDDCTVERFCDSPDGVMLCGSHDGREVYAVTHDLTPTEGWIMQFK  
ISVGCKVSEKIAQNQIHVQYSTDFGVSWNYLVPQCLPADPKCSGSVSQPSVFFPTKGW  
KRITYPLPESLVGNPVRFRFYQKYSMDQWaidNFYLGPGCLDNCRGHGDCLREQCICD  
PGYSGPNCYLTHTLKTLKERFDSEEIKPDLWMSLEGGSTCTECGILAEADTALYFGGST  
VRQAVTQDLDLRGAKFLQYWGRIGSENNMTSCHRPICRKEGVLLDYSTDGGITWTLLH  
EMDYQKYISVRHDYILLPEDALTNTTRLRWWPQFVISNGIVVSGVERAQWALDNLIGGA  
EINPSQLVDTFDDEGTSHEENWSFYPAVRTAGFCGNPSFHLYPNKKKDKTHNALSS  
RELIIQPGYMMQFKIVVGCEATSCGDLHSVMLEYTKDARSDSWQLVQTQCLPSSSNSIG  
CSPFQFHEATYNSVNSSSWKRITIQLPDHVSSSATQFRWIKGEETEKQSWaidHvyig  
EACPKLCSGHGYCTTGAICICDESFGDDCSVFSHDLPsyIKDNFESARVTEANWETIQ  
GGVIGSGCGQLAPYAHGDSLYFNGCQIRQAATKPLDLTRASKIMFVLQIGSMSQTDSCN  
SDLSGPHAVDKAVLLQYSVNNGITWHVIAQHQPkdftQAQRVSYNVPLEARMKGVLLR  
WWQPRHNGTGHDQWALDHVEVVLVSTRKQNYMMNFSRQHGLRHFYNRRRRSLRRY  
P

SEQ ID No:90

MAPLDLDKYVEIARLCKYLPENDLKRLCDYVCDLLLEESNVQPVSTPVTVCGDIHGQFY  
DLCELFRTGGQVPDTNYIFMGDFVDRGYYSLETFTYLLALKAKWPDRTLLRGNHESRQ  
ITQVYGFYDECQTKYGNANAWRYCTKVFDMLTVAALIDEQILCVHGGLSPIKTLQIRTI  
ERNQEIPHKGAFCDLVWSDPEDVDTWaisPRGAGWLFgakVTNEFVHINNKLICRAH

QLVHEGYKFMFDEKLVTVWSAPNYCYRCGNIASIMVFKDVNTREPCLFRAVPDSERVIP  
PRTTTPYFL

SEQ ID No:91

MATRSSRRESRLPFLFTLVALLPPGALCEVWTQRLHGGSAPLPQDRGFLVVQGDPREL  
RLWARGDARGASRADEKPLRRKRSAALQPEPIKVYGGVSLNDSHNQMVVHWAGEKS  
NVIVALARDSLALARPSSDVVVSVDYGKSFKKISDKLNFGLGNRSEAVIAQFYHSPADN  
KRYIFADAYAQYLWITFDFCNTLQGFSIPFRAADLLLHASKASNLLGFDRSHPNKQLWKS  
DDFGQTWIMIQEHVKSFSWGIDPYDKPNTIYIERHEPSGYSTVFRSTDFQSRNQEVIL  
EEVRDFQLRDKYMFATKVHLLGSEQQSSVQLWVSFGRKPMRAAQFVTRHPINEYYIA  
DASEDQVFVCVSHSNRNTNLYISEAEGLKFSLSLENVLYYSPGGAGSDTLVRYFANEPF  
ADFHRVEGLQGVYIATLINGSMNEENMRSVITFDKGGTWEFLQAPAFGTGYGEKINCELS  
QGCSLHLAQRSLQLLNLQLRRMPILSKESAPGLIATGSGVGNLASKTNVYISSSAGARW  
REALPGPHYTTWGDHGGIITAIAQGMETNELKYSTNEGETWKTFFSEKPVFVYGLLTP  
GEKSTVFTIFGSKENVHSLILQVNATDALGVPCTENDYKLWSPSDERGNECLLGHK  
TVFKRRTPHATCFNGEDFDRPVVVSNCSTREDYECDFGFKMSEDLSLEVCVPDPEFS  
GKSYSPVPCPVGSTYRRTGRYRKISGDTCSGGDVEARLEGEVLPCPLAEENEFILYAV  
RKSIYRYDLASGATEQLPLTGLRAAVALDFDYEHNCLYWSDLALDVIQRLCLNGSTGQE  
VIINSGLETVEALAFEPLSQLLYWVDAGFKKIEVANPDGDFRLTIVNSSVLDRPRALVLP  
QEGVMFWTDWGDLPKGIYRSNMDGSAAYHLVSEDVKWPNGISVDDQWIYWTDAYLE  
CIERITFSGQQRSVILDNLPHPYAIAVFKNEIYWDDWSQLSIFRASKYSGSQMEILANQLT  
GLMDMKIFYKGKNTGSNACVPRPCSLCLPKANNRSRSCRPEDVSSSVLPSGDLMCD  
CPQGYQLKNNTCVKEENTCLRNQYRCSNGNCINSIWWCDFDNDCGDMSDERNCPTTI  
CDLDTQFRQCQESGTCIPLSYKCDLEDDCGDNSDESHCEMHQCRSDEYNCSSGMCIRS  
SWVCDGDNDNCRDWSDEANCTAIYHTCEASNFCRNGHCIPQRWACDGDGDCQDGS  
DEDPVNCEKKCNGFRCPNGTCIPSSKHCDGLRDCSDGSDEQHCEPLCTHFMDFVCKN  
RQQCLFHSMVCDGIIQCRDGSDEDAAFAGCSQDPEFHKVCDEFQGCQNGVCISLIWK  
CDGMDDCGDYSDAENCENPTEAPNCSRYFQFRCENGHCIPNRWKCDRENDGCDWS  
DEKDCGDSHILPFSTPGPSTCLPNYYRCSSGTCVMDTWVCDGYRDCADGSDEEACPL  
LANVTAASTPTQLGRCDRFEFECHQPKTCIPNWKRCDCGHQDCQDGRDEANCPHSTL  
TCMSREFQCEDGEACIVLSERCDGFLDCSDESDEKACSDELTVYKVQNLQWTADFSG  
DVTLTWMRPKKMPSASCVYNVYRVVGESIWKLTETHSNKTNVTLKVLKPDTTYQVKV  
QVQCLSKAHNTNDFVTLRTPEGLPDAPRNLQLSLPREAEGVIVGHWAPPIHTHGLIREYI  
VEYSRSGSKMWASQRAASNFTIKNLLVNTLYTVRVAAVTSRGIGNWSDSKSITTIGK

VIPPPDIHIDSYGENYLSFTLTMESDIKVNGYVNLFWAFDTHKQERRTLNFRGSILSHKV  
 GNLTHTSYEISAWAKTDLGDSPLAFEHVMTRGVRPPAPSLKAKAINQTAVECTWTGP  
 RNVVYGIFYATSFLDLYRNPksLTtSLHNKTVIVSKDEQYLFLVRVVPYQGPSSDYVVV  
 KMIPDSRLPPRHLHVHTGKTSVIKWESPYDSPDQDLYAIAVKDLIRKTDRSYKVKS  
 NSTVEYTLNKLEPGGKYHIIVQLGNMSKDSSIKITTVSLAPDALKIITENDHVLLFWKSLA  
 LKEKHFNESRGYIEHMFDSAMNITAYLGNTTDNFFKISNLKMGHNYTFTVQARCLFGNQI  
 CGEPAILLYDELGSGADASATQAARSTDVAVVVPILFLILLSLGVGFAILYTKHRRQLSS  
 FTAFA NSHYSSRLGSAIFSSGDDLGEDDEDAPMITGFSDDVPMVIA

SEQ ID No:92

MEGASFGAGRAGAALDPVSFARRPQTLLRVASWVFSIAVFGPIVNEGYVNTDSGPELR  
 CVFNGNAGACRFGVALGLGAFLACAAFLLLDVRFQQISSVRDRRRRAVLLDLGFSGLWS  
 FLWFGVFCFLTQWQRTAPGPATTQAGDAARAAIAFSFFSILSWVALTVKALQRFRLGT  
 DMSLFATEQLSTGASQAYPGYPVGSVEGTETYQSPFFTETLDTSPKGYQVPAY

SEQ ID No:93

MKDRTQELRTAKDSDDDDDDVAVTVD RDRFMDEFFEQVEEIRGFIDKIAENVEEVKRKHS  
 AILASPNPDEKTKEELEELMSDIKKTANKVRSKLKSIEQSIEQEEGLNRSSADLRIRKTQH  
 STLSRK FVEVMSEYNATQSDYRERCKGRIQRQLEITGRTTTSEELEDMLESGNPAIFAS  
 GIIMDSSISKQALSEIETRHSEIIKLENSIRELHDMFMDMAMLVESQGEMIDRIEYNVEHAV  
 DYVERAVSDTKKAVKYQSKARRKKIMIIICCVILGIVIASTVGGIFA

SEQ ID No:94

MVLWRRSRYLLREIEAQWSISALWEGFQKWRDNLFLQIVQLIQHVYSVWTASRTVFIKII  
 VTRHTSTGGGFCDCGDTEAWKTGPFCVNHEPGRAGTIKENSRCPLNEEVIVQARKIFP  
 SVIKYVEMTIWEEEEKELPPELQIREKNERYCYVLFNDEHHSYDHVIYSLQRALDCELA  
 AQLHTTAIDKEGRRAVKAGAYAACQEAKEDIKSHSENV SQHPLHVEVLHSEIMAHQKFA  
 LRLGSWMNKIMSYS SDFRQIFCQACLREEPDSENPC LISRLMLWDAKLYKGARKILHELI  
 FSSFFMEMEYKKLFAMEFVKYKQLQKEYISDDHDRSISITALSVQMFTVPTLARHLIEE  
 QNVISVITETLLEVLPEYLD RNNKFNFQGYSDKLGRVYAVICDLKYILISKPTIWTERLR  
 MQFLEGFRSFLKILTCMQGMEEIRRQVGQHIEVDPDWEAAIAIQMQLKNILLMFQEWCA  
 CDEELLLVAYKECHKAVMRCSTSFISSSKTVVQSCGHSLET KSYRVSEDLVSIHLPLSRT  
 LAGLHVRLSRLGAVSRLHEFVSFEDFQVEVLVEYPLRCLVLVAQVVAEMWRRNGLSLIS

QVFYYQDVKCREEMYDKDIIMLQIGASLMDPNKFLLLVLQRYELAEAFNKTISTKDQDLIK  
QYNTLIEEMLQVLIYIVGERYVPGVGNVTKEEVTMREIHLCCIEPMPHSAIAKNLPEN

SEQ ID No:95

MKALRLSASALFCLLLINGLGAAPPGRPEAQPPPLSSEHKEPVAGDAVPGPKDGSAP  
RGARNSEPQDEGELFQGVDPRALAAVLLQALDRPASPPAPSGSQQGPEEEAAEALLTE  
TVRSQTHSLPAAGEPEPAAPPRPQTPENGPEASDPSEELEALASLLQELRDFSPSSAK  
RQQETAAAETETRHTLTRVNLESPGPERVWRASWGEFQARVPERAPLPPPAPSQFQ  
ARMPDSGPLPETHKFGEGVSSPKTHLGEALAPLSKAYQGVAAPFPKARRAESALLGGS  
EAGERLLQQGLAQVEAGRRQAEATRQAAAQEERLADLASDLLLQYLLQGGARQRLG  
GRGLQEAAEERESAREEEEEAEQERRGGEERVGEEDDEAAEAAEAEADEAERARQNAL  
LFAEEEDGEAGAEDKRSQEETPGHRRKEAEGTEEGGEEEDDEEMDPQTIDSLIELSTK  
LHLPADDVVSIIIEVEEKRNRRKKAPPEPVPPPRAAPATHVRSPQPPPPPPPSARDELP  
DWNEVLPPWDREEDDEVYPPGPYHFPNYIRPRTLQPPSALRRRHHYHALPPSRHYPG  
REAQARHAQQEEAAEERRLQEQQELENYIEHVLLRRP

SEQ ID No:96

MAHRKLESVSGSMLDHRVRPGVPVPHSQEPESEDMELPLEGYVPEGLELAALRPESPA  
PEEQECHNHSPDGDSSSDYVNNTSEEDYDEGLPEEEEGITYYIRYCPEDDSYLEGMD  
CNGEEYLAHSAHPVDTDECQEAVEEWTD SAGPHPHGHEAEGSQDYPDGQLPIPEDEP  
SVLEAHDQEEDGHYCASKEGYQDYYPEEANGNTGASPYRLRRGDGDLEDQEEDIDQI  
VAEIKMSLSMTSITSASEASPEHGPEPGPEDSVEACPPIKASCSPSRHEARPKSLNLLPE  
AKHPGDPQRGFKPKTRTPEERLKWPHQVCNGLEQPRKQQRSDLN GPVDNNNIPETK  
KVASFPSFVAVPGPCEPEDLIDGIIFAANYLGSTQLLSERNPSKNIRMMQAQEA VSRVKR  
MQKAAKIKKKANSEGDAQTLTEVDLFISTQRIKVLNADTQETMMDHALRTISYIADIGNIV  
VLMARRRMPRSASQDCIETTPGAQEGKKQYKMICHVFESEDAQLIAQSIGQAFSVAYQ  
EFLRANGINPEDLSQKEYSDIINTQEMYNDLIHFSNSENCKELQLEKHKGEILGVVVE  
SGWGSILPTVILANMMNGGPAARSGKLSIGDQIMSINGTSLVGLPLATCQGGIIKGLKNQT  
QVKLNIVSCPPVTTVLIKRPDLKYQLGFSVQNGIICSLMRGGIAERGGVRVGHRIIEINGQ  
SVVATAHEKIVQALSNSVGEIHMKTMPAAMFRLTGQETPLYI

SEQ ID No:97

MDTSSVGGLELTDQTPVLLGSTAMATSLTNVGNSFSGPANPLVSRSNKFQNSSVEDDD  
DVVFIQVQPPPPSVPVVADQRTITFTSSKNEELQGNDKITPSSKELASQKGSVSETIVI

DDEEDMETNQGQEKNSSNFIERRPPETKNRTNDVDFSTSSFSRSKVNAGMGNSGITTE  
 PDSEIQIANVTTLETGVSSVNDGQLENTDGRDMNLMITHVTSLQNTNLGDVSNGLQSSN  
 FGVNIQTYTPSLTSQTKTGVPFPNPGRMNVAGDVFQNGESATHHNPDSWISQSASFPR  
 NQKQPGVDSLSPVASLPKQIFQPSVQQQPTKPVKVT CANCKKPLQKGQTAYQRKGS A  
 HLCSTTCLSSFSHKPAPKKLCVMCKKDITTMKGTIVAQVDSSESFQEF CSTSCLSLYED  
 KQNPTKGALNKSRTCIGKLTEIRHEVSFKNMTHKLCSDHCFNRYRMANGLIMNCCEQ  
 CGEYLPSKGAGNNVLVIDGQQKR FCCQSCVSEYKQVGSHPSFLKEVRDHMQDSFLMQ  
 PEKYGKLTCTGCR TQCRFFDMTQCIGPNGYMEPYCSTACMNSHKTKYAKS QSLGIIC  
 HFCKRNSLPQYQATMPDGKLYNFCNSSCVAKFQALSMQSSPNGQFVAPSDIQLKCN Y  
 CKNSFC SKPEILEWENKVHQFCSKTCSDDYKKLHCIVTYCEYCQEEKTLHETVNFSGVK  
 RPF CSEGCKLLYKQDFARRLG LRCVTCNYCSQLCKKGATKELDGVRDFCSEDCKKF  
 QDWYYKAARCDCKSQGTLKERVQWRGEMKHFC DQHCLLRFYCQQNEPNMTTQKG  
 PENLHYDQGCQTSRTKMTGSAPPPSPTPNKEMKNKAVLCKPLTMTKATYCKPHMQTK  
 SCQTDDTWRT EYVPVPIPVVYIPVPMHMY SQNIPVPTTVPVVPVFLPAPLDSSEKI  
 PAAIEELKSKVSSDALDTELLTMTDMMSEDEGKTETTNINSVIIETDIIGSDLLKNSDPETQ  
 SSMPDV PYPEDLDIEIDFPRAAEELDMENEFLLPVFGEEYEEQPRPRSKKKGAKRKAV  
 SGYQSHDDSSDNSECSFPFKYTYGVNAWKHWVKTRQLDEDLLVLDELKSSKSVKLKE  
 DLLSHTTAELNYGLAHFVNEIRRPNGENYAPDSIYYLCLGIQEYLCGSNRKDNIFIDPGY  
 QTFEQELNKILRSWQPSILPDGSIFSRVEEDYLWRIKQLGSHSPVALLNTLFYFNTKYFG  
 LKTVEQHLRLSFGTVFRHWKKNPLTMENKACLRYQVSSLCGTDNEDKITTGKRKHEDD  
 EPVFEQIENTANPSRCPVKMFECYLSKSPQNLNQRMDVFY LQPECSSSTDSPVWYTST  
 SLDRNTLENMLVRVLLVKDIYDKDNYELDEDTD

SEQ ID No:98

MLSLDFLDDVRRMNKRQLYYQVLNFGMIVSSALMIWKGLMVITGSESPIVVLSGSMEP  
 AFHRGDLLFLTNRVEDPIRVGEIVVFRIEGREIPIVHRVLKIHEKQNGHIKFLT KGDNNAVD  
 DRGLYKQGQHWLEKKDVVGRARGFVPYIGIVTILMNDYPKFYAVLFLGLFVLVHRE

SEQ ID No:99

AESDLQLAQIKCNLGRAVQLQELWPGGLFWTRKLS TYIRLYGRKFSKEDHVLFIKLLYEL  
 VSIPKLEISMMQGFARLLINLLKKKELLSRADLELPWRPLYDMVERILYSKTEHLGLNWFP  
 NSVENILKTLVKSCRPYFPADATAEMLEEW RPLMCPFDVTMQKAITYFEIFLPTSLPPEL  
 HHKGFKLWFDELIGLWVSVQNL PQWEGQLVNL FARLATDNIGYIDWDPYVPKIFTRILRS  
 LNLPGSSQVLVPRFLT NAYDIGHAVIWITAMMGGPSKLVQKHLAGLFNSITSFYHPSNN

GRWLNKLMKLLQRLPNSVVRRLHRERYKKPSWLTPVPDSHKLTDQDVTDFVQCIIQPV  
LLAMFSKTGSLEAAQALQNLALMRPELVIPPVLERTYPALETLTEPHQLTATLSCVIGVAR  
SLVSGGRWFPEGPTHMLPLLMRALPGVDPNDFSKCMITFQFIATFSTLVPLVDCSSVLQ  
ERNDLTEVERELCSATAEFEDFVLQFMDRCFGLIESSTLEQTREETETEKMTHLESLEVEL  
GLSSTFSTILTQCSKEIFMVALQKVFNFSTSHIFETR VAGRMVADM CRAAVKCCPEESLK  
LFVPHCCSVITQLTMNDDVLNDEELD KELLWNLQLLSEITRVDGRKLLLYREQLVKILQR  
TLHLTCKQGYTLSCNLLHLLRSTTLIYPT EYCSVPGGFDKPPSEYFPIKDWGKPGDLW  
NLGIQWHVPSSEEVSAFYLLDSFLQPELVKLQHCGDGKLEMSRDDILQSLTIVHNCLIG  
SGNLLPPLKGEPVTNLVPSMVSLEETKLYTGLEYDLSRENHREVIATVIRKLLNHILDNSE  
DDTKSLFLIIKIIGDLLQFQGSCHKHEFDSRWKSFNLVKKSMENRLHGKKQHIRALLIDRVM  
LQHELRTLTVEGCEYKKIHQDMIRDLLRLSTSSYSQVRNKAQQTFFAALGAYNFCCRDII  
PLVLEFLRPDRQGVTQQQFKGALYCLLGNHSGVCLANLHDWDCIVQTWPAIVSSGLSQ  
AMSLEKPSIVRLFDDLAEKIHRQYETIGLDF TIPKSCVEIAELLQQSKNPSINQILLSPEKIK  
EGIKRQQEKNADALRNYENLVDTLLDGVEQRNLPWKFEHIGIGLLSLLLRDDRVLPLRAI  
RFFVENLNHDAIWRKMAISAVAGILKQLKRTHKKLTINPCEISGCPKPTQIIAGDRPDNH  
WLHYDSKITPRTKKEWESSCFVEKTHWGYTWPKNMVVYAGVEEQPKLGRSREDMT  
EAEQIIFDHFSDPKFVEQLITFLSLED RKGKDKFNPRRFCLFKGIFRNFD DAFLPVLPKPHL  
EHLVADSHESTQRCVAEIIAGLIRGSKHWT FEKVEKLWELLCP LLRTALS NITVETYNDW  
GACIATSCESRDPRKLHWLFELLLESPLSGEGGSFVDACRLYVLQGGLAQQEWVRPEL  
LHRLKYLEPKLTQVYKNVRERIGSVLTYIF MIDVSLPNTTPTISPHVPEFTARILEK LKPL  
MDVDEEIQNHVMEENGIGEEDE RTQG ILLKTI LKWL MASAGRSFSTAVTEQLQLLPLFF  
KIAPVENDNSYDELKRDAKLCLSLMSQGLLYPHQVPLVLQVLKQTARSSSWHARYTVLT  
YLQTMVFYNLFIFLNNEDAVKDIRWLVISLLEDEQLEVREMAATTL SGLLQCNFLTMDSP  
MQIHFEQLCKTKLPKKRKRDPGSGDTIPSAELVKRHAGVLGLGACVLS SPYDVPTWM  
PQLLMNLSAHLNDPQPIEMTVKKTLSNFRRTHHDNWQE HKQQFTDDQLLVLTDLLVSP  
CYA

SEQ ID No:100

GNIFGNLLKSLIGKKEMRILMVGLDAAGKTTILYK LKLG EIVTTIPTIGFNVETVEYKNISFT  
VWDVGGQDKIRPLWRHYFQNTQGLIFVDSNDRERVNEAREELMRMLAEDEL RDAVL  
LVFANKQDLPNAMNAAEITDKLGLHSLRHRN WYIQATCATSGDGLYEGLDWLANQLKN  
KK

SEQ ID No:101

MDLEGDRNGGAKKKNFFKLNNKSEKDKKEKKPTVSVFSMFRYSNWLDKLYMVVGTLA  
 AIIHGAGLPLMMLVFGEMTDIFANAGNLEDLMSNITNRSDINDTGFFMNLEEDMTRYAYY  
 YSGIGAGVLVAAYIQVSFWCLAAGRQIHKIRKQFFHAIMRQEIGWFDVHVDVGELNTRLTD  
 DVSKINEGIGDKIGMFFQSMATFFTGFIVGFTRGWKLTVLILAISPVLGLSAAVWAKILSSF  
 TDKELLAYAKAGAVAEVLAAIRTVIAFGGQKKELERYNKNLEEAKRIGIKKAITANISIGA  
 AFLLIYASYALAFWYGTTLVLSGEYSIGQVLTVFFSVLIGAFSVGQASPSIEAFANARGAA  
 YEIFKIIDNKPSIDSYSKSGHKPDNIKGNLEFRNVHFSYPSRKEVKILKGLNLKVQSGQTV  
 ALVGNSGCGKSTTVQLMQRLYDPTEGMVSVGDQDIRTINVRFLREIIGVVSQEPVLFAT  
 TIAENIRYGRENTVMDEIEKAVKEANAYDFIMKLPKFDTLVGERGAQLSGGQKQRIAA  
 RALVRNPKILLLDEATSALDTESEAVVQVALDKARKGRTTIVIAHRLSTVRNADVIAGFDD  
 GVIVEKGNHDELMKEKGIYFKLVTMQTAGNEVELENAADESKSEIDALEMSSNDSRSSLI  
 RKRSTRRSVRGSQAQDRKLSTKEALDESIPVSVFWRIMKLNLTWPYFVVGVFCAIING  
 GLQPAFAIIFSKIIGVFTRIDDPETKRQNSNLSLLFLALGIISFITFFLQGFTFGKAGEILTK  
 RLRYMVFRSMLRQDVSWFDDPKNTTGALTTRLANDAAQVKGAIGSRLAVITQNIANLGT  
 GIIISFIYGWQLTLLLAIVPIIAIAGVVEMKMLSGQALKDKKELEGAGKIAIEAENFRTVVS  
 LTQEQKFEHMYAQSLQVPYRNSLRKAHIFGITFSFTQAMMYFSYAGCFRFGAYLVAHKL  
 MSFEDVLLVFSVAVFGAMAVGQVSSFAPDYAKAKISAHHIIMIEKTPLIDSYSTEGLMPN  
 TLEGNVTFGEVVFNYPTRPDIPVLQGLSLEVKKGQTLALVGSSGCGKSTVVQLLERFYD  
 PLAGKVLLDGKEIKRLNVQWLRAHLGIVSQEPILFDCSIAENIAYGDNSRVVSQEEIVRAA  
 KEANIHAIESLPNKYSTKVGDGTQLSGGQKQRIAIARALVRQPHILLLDEATSALDTES  
 EKVVEALDKAREGRTCIVIAHRLSTIQNADLIVVFQNGRVKEHGTHQQLLAQKGIYFSM  
 VSVQAGTKRQ

SEQ ID No:102

MFSLSSTVQPQFTVPLSHLINAFTPKNTSVSLSGVSVSQNQHRDVVPEHEAPSSECM  
 FSDFLTCLNIVSIGKGKIFEGYRSMFMEPAKRMKKSOLDTNDNWHIRPEPFSLSIPPSLNL  
 DLGLSELKIGQIDQLVENLLPGFCKGKNISHWHTSHVSAQSFFENKYGNLDIFSTLRSS  
 CLYRHHSRALQSICSDLQYWPVFIQSRGFKTLKSRTTQLSTSERLAETQNIAPSFVKG  
 FLLRDRGSDVESLDKLMKTKNIPEAHQDAFKTGFAEGFLKAQALTQKTNDLSLRTRLILF  
 VLLFGIYGILLKNPFLSVRFRTTTGLDSAVIDPVQMKNVTFEHVKGVEEAKQELQEVVEF  
 LKNPQKFTILGGKLPKGILLVGPPGTGKTLARAVAGEADVPFYYASGSEFDEMFGVVG  
 ASRIRNLFREAKANAPCVIFIDELDSVGGKRIESPMHPYSRQTINQLLAEMDGFKNPNEG  
 IIGATNFPEALDNALIRPGRFDMQVTVPRPDVKGRTEILKWYLNKIKFDQSVDPETIARGT  
 VGFSGALENLVNQAALKAADVKGEMVTMKELEFSKDKILMGPERRSVEIDNKNKTITA

YHESGHAIAYYTKDAMPINKATIMPRGPTLGHVSLLPENDRWNETRAQLLAQMDVSMG  
GRVAEELIFGTDHITTGASSDFDNATKIAKRMVTKFGMSEKLGVM TYSDTGKLS PETQS  
AIEQEIRILLRDSYERAKHILKTHAKEHKNLAEALLTYETLDAKEIQIVLEGKKLEVR

SEQ ID No:103

METPAAAAPAGSLFPSFLLLACGTLVAALLGAAHRLGLFYQLLHKVDKASVRHGGGENVA  
AVLRAHGVRFIFTLVGGHISPLL VACEKLGIRVVDTRHEVTAVFAADAMARLSGTVGVA  
V TAGPGLTNTVTAVKNAQMAQSPILLGGAASTLLQNRGALQAVDQLSLFRPLCKFCVS  
VRRVRDIVPTLRAAMAAAQSGTPGPVFVELPVDVLYPYFMVQKEMVPAKPPKGLVGRV  
VSWYLENYLANLFAGAWEPQPEGPLPLDIPQASPPQQVQRCVEILSRAKRPLMVLGSQA  
LLTPTSADKLRAAVETLGVPCFLGGMARGLLGRNHPLHIRENRS AALKKADVIVLAGTVC  
DFRLSYGRVLSSHSSKIIIVNRNREEMLLNSDIFWKPQEAVQGDVGSFVLKLVEGLQGQT  
WAPDWVEELREADRQKEQTFREKAAMPVAQHLNPVQVLQ LVEETLPDNSILVVDGGD  
FVGTAHLVQPRGPLRWLDPGAFGTLGVGAGFALGAKLCRPDAE VWCFLFGDGAFGYS  
LIEFDTFVRHKIPVMALVGNDAGWTQISREQVPSLGSNVACGLAYTDYHKAAMGLGAR  
GLLSRENEDQVVKVLHDAQQQCRDGHPVVVNILIGRTDFRDGSI AV

SEQ ID No:104

MPVLSRPRPW RGNTLKRTAVLLALAAYGAHKVYPLVRQCLAPARGLQAPAGEPTQEAS  
GVAAAKAGMNRVFLQRLLWLLRLLFPRVLCRETGLLALHSAALVSRTFLSVYVARLDGR  
LARCIA RKDPRAFGWQLLQWLLIALPATFVNSAIRYLEGQLALSFRSRLVAHAYRLYFSQ  
QTYRVS NM DGRLRNP DQSLTEDVVAFAASVAHLYSNLTKPLLDVAVTSY TLLRAARSR  
GAGTAWPSA IAGLVVFLTANVLRAFSPKFGELVAEEARRKGELRYMHSRVVANSEEIAF  
YGGHEVELALLQRSYQDLASQINLILLERLWYVMLEQFLMKYVWSASGLLMVAVPIITAT  
GYSESDAEAVKKA ALEKKEEELV SERTEAFTIARNLLTAAADA IERIMSSYKEVTELAGYT  
ARVHEMFQVFEDVQRCHF KRP RELEDAQAGSGTIGRSGVRVEGPLKIRGQVVDVEQGI  
ICENIPIVTPSGEVVVASLNIRVEEGMHLLITGPNGCGKSSLFRILGGLWPTYGGVLYKPP  
PQRMFYIPQRPYMSVGSRLRDQVIYPDSVEDMQRKGYSEQDLEAILDVVHLHHILQREG  
GWEAMCDWKDVL SGGEKQRIGMARMFYHRPKYALLDECTSAVSIDVEGKIFQAAKDA  
GIALLSITHRPSLWKYHTHLLQFDGEGGWKFEKLD SAARLSL TEEKQRLEQQLAGIPKM  
QRRLQELCQILGEAVAPAHVPAPSPQGPGGLQGAST

SEQ ID No:105

MGTVHARSLEPLPSSGPDFGGLGEEAEFVEVEPEAKQEILENKDVVVQHVHFDGLGRT  
KDDIIICEIGDVFKAKNLIEMRKSHEAREKLLRLGIFRQVDVLIDTCQGDDALPNGLDVTF  
EVTELRRLTGSYNTMVGNNEGSMVLGLKLPNLLGRAEKVTFQFSYGTKETSYGLSFFK  
PRPGNFERNFSVNLYKVTGQFPWSSLRETDRGMSAEYSFPIWKTSHTVKWEGVWREL  
GCLSRITASFAVRKESGHSLSKSSLSHAMVIDSRNSSILPRRGALLKVNQELAGYTGGDVS  
FIKEDFELQLNKQLIFDSVFSASFVGGMVPIGDKPSSIADRFYLGGPSTVRGFSMHSIG  
PQSEGDYLGGEAYWAGGLHLYTPLFRPGQGGFGELFRTHFFLNAGNLCNLNYGEGP  
KAHIRKLAECIRWSYGAGIVLRLGNIARLELNYCVPMPGVQTDGDRICDGVQFGAGIRFL

SEQ ID No:106

GSRASTLLRDEELEEIKKETGFSHSQITRLYSRFTSLDKGENGTLSREDFQRIPELAINPL  
GDRIINAFFPEGEDQVNFRGFMRTLAHFRPIEDNEKSKDVNGPEPLNSRSNKLHFAFRL  
YDLKDDEKISRDELLQVLRMMVGVNISDEQLGSIADRTIQEADQDGDSAISFTEFVKVLE  
KVDVEQKMSIRFLH

SEQ ID No:107

MASESSPLLAYRLLGEEGVALPANGAGGPGGASARKLSTFLGVVPTVLSMFSIVVFLRI  
GFVVGHAGLLQALAMLLVAYFILALTVLSVCAIATNGAVQGGGAYFMISRTLGPVEVGSI  
GLMFYLANVCGCAVSLLGLVESVLDVFGADATGPSGLRVLPQGYGWNLLYGSLLLGLV  
GGVCTLGAGLYARASFLTFLLVSGSLASVLISFVAVGPRDIRLTPRPGPNGSSLPPRFGH  
FTGFNSSTLKDNLGAGYAEDYTTGAVMNFANVFAVLNFGCTGIMAGANMSGELKDPSR  
AIPLGTIVAVAYTFFVYVLLFFLSSFTCDRTLQEDYGFFRAISLWPPLVLIGIYATALSAS  
MSSLIGASRILHALARDDLFGVILAPAKVVSRRGNPWAAVLYSWGLVQLVLLAGKLNLA  
AVVTVFYLVAYAAMDLSCLSLEWASAPNFRPTFSLSWHTCLLGVASCLLMMFLISPGA  
AGGSLLLMGLLAALLTARGGPSSWGYVSQALLFHQVRKYLLRLDVRKDHVKFWRPQLL  
LLVGNPRGALPLRLANQLKKGGLYVLGHVTLGDLSLPSDPVQPQYGAWLSLVDRAQ  
VKAFVDLTFSPSVRQGAQHLLRISGLGGMKPNTLVLGFYDDAPPQDHFLTDPAFSEPAD  
STREGSSPALSTLFPPPRAPGSPRALNPQDYVATVADALKMNKNVVLARASGALPPER  
LSRSGSGGTSQLHHVDVWPLNLLRPRGGPGYVDVCGFLFLLQMATILGMVPAWHSARLRI  
FLCLGPREAPGAAEGRLRALLSQLRIRAEVQEVVWGEGAGAGEPEAEEEGDFVNNGR  
GDAEAEALARSANALVRAQQGRGTGGGPGGPEGGDAEGPITALTFLYLPRPPADPAR  
YPRYLALLETLTRDLGPTLLVHGVTPVTCTDL

SEQ ID No:108

MASFVTEVLAHSGRLEKEDLGTRISRLTRRVEEIKGEVCNMISKKYSEFLPSMQSAQGLI  
 TQVDKLSEDIDLLKSRIESEVRRDLHVSTGEFTDLKQQLERDSVVL SLLKQLQEFSTAIEE  
 YNCALTEKKYVTGAQRLEEAQKCLKLLKSRKCFDLKILKSLSMELTIQKQNILYHLGEEW  
 QKLIVWKFPFSKDTSSLESYLQTELHLYTEQSHKEEKTMPPISSVLLAFSVLGELH SKL  
 KSFGQMLLKYILRPLASCP SLHAVIESQPNIVIIRFESIMTNLEYPSPSEVFTKIRLVLEVLQ  
 KQLLDLPLD TDLENEKTSTVPLAEMLGDMIWEDLSECLIKNCLVYSIPTNSSKLQQYEEII  
 QSTEEFENALKEMRFLKGD TTDLLKYARNINSHFANKKCQDVIVAARNLMTSEIHNTVKII  
 PDSKINVP ELPTPDEDNKLEVQKVSNTQYHEVMNLEPENTLDQHSFSLPTCRISES VKK  
 LMELAYQTLLEATTSSDQCAVQLFYSVRNIFHLFHDVPTYHKENLQKLPQLAAIHNNNC  
 MYIAHHLLTLGHQFRLRLAPILCDGTATFVDLVPGFRRLGTECF LAQMR AQKGELLERLS  
 SARNFSNM DDEENYSAASKAVRQVLHQLKRLGIVWQDVL PVNIYCKAMGTLLNTAISEV  
 IGKITALEDISTEDGDRLYSLCKTVMDEGPQVFAPLSEESKNKKYQEEVPVYVPKWM PF  
 KELMMMLQASLQEIGDRWADGKGPLAAAFSSSEVKALIRALFQNTERRAAALAKIK

SEQ ID No:109

MSRLGALGGARAGLG LLLGTAAGLGFLCLLYSQRWKRTQRHGRSQSLPNSLDYTQTS  
 DPGRHVMLLRAPVPGGAGDASVLP SLPREGQEKVLDRLDFVLTSLVALRREVEELRSSL  
 RGLAGEIVGEVRCHMEENQRVARRRRRFPFVRERSDSTGSSSVYFTASSGATFTDAESE  
 GGYTTANAESDNERDSDKESEDGEDEVSCETVKMGRKDSL DLEEEAASGASSALEAG  
 GSSGLEDVLP LLQQADELHRGDEQKGREGFQ LLLNNKL VYGSRQDFLWRLARAYS DM  
 CELTEEVS EKKSYALDGKEEA EAALEKGD ESADCHLWYAVLCGQLAEHESIQRRIQSGF  
 SFKEHVDKAIALQPENPMAHFLLGRWCYQVSHLSWLEKKTATALL ESPLSATVEDALQS  
 FLKAEELQPGFSKAGRVYISKCYRELGKNSEARWWMKLAL ELPDVT KEDLAIQKDLEEL  
 EVILRD

SEQ ID No:110

MENHKSNNKENITIVDISRKINQLPEAERNLLENGSVYVGLNAALCGLIANS LFRRILNVT  
 KARIAAGLPMAGIPFLT TDLTYRCFVSFPLNTGDLDCETCTITRSGLTGLVIGGLYPVFLAI  
 PVNGGLAARYQSALLPHKGNILSYWIRT SKPVFRKMLFPILLQTMFSAYLGSEQYKLLIK  
 ALQLSEPGKEIH

SEQ ID No:111

DLRRQLLSGHLTQDQVREVKRHITVRLDWGNEHLGLDLVPRKDFEVVDSQISVSDLY  
 KMHLSRQSVQQSTSQVDTMRPRHGETCRMPVPHHFFLSLKSF TYNTIGEDTDVFFSL

YDMREGKQISERFLVRLNKNNGGPRNPEKIERMCALFTDLSSKDMKRDLYIVAHVIRIGR  
MLLNDSSKKGPPHLHYRRPYGCAVLSILDVLQSLTEVKEEKDFVLKVYTCNNESEWSQIH  
ENIIRKSSAKYSAPSASHGLIISLQLLRGDMEQIRRENPMIFNRGLAITRKLGFDPVIMPGD  
IRNDLYLTLEKGDFFERGGKSVQKNIEVTMYVLYADGEILKDCISLGSGEPNRSSYHSFVL  
YHSNSPRWGEEIKLPIPIDRFRGSHLRFEFRH CSTKD KGEKKLFGFAFSTLMRDDGTTLS  
DDIHELIVYKCDENSTFNNHALYLGLPCKEDYNGCPNIPSSLIFQRSTKESFFISTQLSS  
TKLTQNVDLLALLKWKAFDPDRIMDVLGRLRHVSGEEIVKFLQDILDTL FVILDDNTEKYGL  
LVFQSLVFIINLLRDIKYFHFRPVM DTYIQKH FAGALAYKELIRCLKWYMDCSAELIRQDHI  
QEAMRALEYLFKFIVQSRILYSRATCGMEEEQFRSSIQELFQSIRFVLSLDSRNSETLLFT  
QAALLNSFPTIFDELLQMFTVQEVAEFVRGTLGSM PSTVHIGQSMDVVKLQSIARTVDS  
RLFSFSESRRILLPVVLHHIHLHLRQQKELLICSGILGSIFSIVKTSSLEADVMEEVEMMVE  
SLLDVLLQTLLTIMSKSHAQEA VRGQRCPQCTAEITGEYVSCLLSLLRQMCDTHFQHLL  
DNFQSKDELKEFLLKIFCVFRNLMKMSVFP RDWMVMRLLTSNIIVTTVQYLSSALHKNFT  
ETDFDFKVWNSYFSLAVLFINQPSLQLEIITS AKRKKILD KYGDMRVMMAYELFSMWQN  
LGEHKIHFIPGMIGPFLGVTLVPQPEVRNIMIP IFHDMMDWEQRKNGNFKQVEAELIDKL  
DSMVSEGKGDESYRELFSLLTQLFGPYPSLLEKVEQETWRETGISFVTSVTRLMERLLD  
YRDCMKGEETENKKIGCTVNL MNFYKSEINKEEMYIRYI HKLCDMHLQAENYTEAAFTLL  
LYCELLQWEDRPLREFLHYP SQTEWQRKEGLCRKIIHYFNKGKSW EFGIPLCRELACQY  
ESLYDYQSLSWIRKMEASYDNIMEQQRLEPEFFRVGFYGRKF PFFLRNKEYVCRGHD  
YERLEAFQQRMLSEFPQAVAMQH PNHPPDAILQCDAQYLQIYAVTPIPDYVDVLQMDR  
VPDRVKSFYRVNNVRKFRYDRPFHKGPKDKENEFKSLWIERTTLTLTHSLPGISRWF EV  
ERRELVEVSPL ENAIQVVENKNQELRSLISQYQHKQVHGNINLLSMCLNGVIDAAVNGGI  
ARYQEAF FDKDYINKHPGDAEKITQLKELMQEQVHVLGVGLAVHEKFVHP EMRPLHKKL  
IDQFQMMRASLYHEFPGLDKLSPACSGTSTPRGNVLASHSPMSPESIKMTHRHSPMNL  
MGTGRHSSSSSLSSHASSEAGNMV MLGDGSMGDAPEDLYHHMQLAYPNPRYQGSVTN  
VSVLSSSQASPSSSSLSSTHSAPSQMITSAPSSARGSPSLPD KYRHAREMMLLLPTYRD  
RPSSAMYPAAILENGQPPNFQRALFQQVVGACKPCSDPNLSVAEKGHYSLHFDAFHHP  
LGDTPPALPARTLRKSPLHIPASPTSPQSGLDG SNSTLSGSASSGVSSLSSES NFGHSS  
EAPPRDTMDSMPSQAWN ADEDLEPPYLPVHYSLS ESAVLDSIKAQPCRSHSAPGCVI  
PQDPM DPPALPPKPYHPRLPALEHDEGVLLREETERPRGLHRKAPLPPGSAKEEQARM  
AWEHGRGEQ

MAATFFGEVVKAPCRAGTEDEEEEEEGRRETPEDREVRLQLARKREVRLRRQTKTSL  
EVSLLKYPCKFIIAIGNNAVAFLSSFVMNSGVWEEVGCAKLWNEWCRTTDTTHLSST  
EAFCVFYHLKSNPSVFLCQCSCYVAEDQQYQWLEKVFGSCPRKNMQITILTCRHVTDY  
KTSESTGSLPSPFLRALKTQNFKDSACCPLEQPNIVHDLPAAVLSYCQVWKIPAILYLC  
YTDVMKLDLITVEAFKPILSTRSLKGLVKNIPQSTEILKKLMTTNEIQSNIYT

SEQ ID No:113

MSWVQATLLARGLCRAWGGTCGAALTGTSISQVPRRLPRGLHCSAAHSSEQSLVPS  
PPEPRQRPTKALVPFEDLFGQAPGGERDKASFLQTVQKFAEHSVRKRGHIDFIYLALRK  
MREYGVERDLAVYNQLLNIFPKEVFRPRNIIQRIFVHYPRQQECGIAVLEQMENHGVMP  
NKETEFLLIQIFGRKSYPMKLVLRLKLWFPRFMNVNPFVPRDLPQDPVELAMFGLRHM  
EPDLSARVTIYQVPLPKDSTGAADPPQPHIVGIQSPDQQAALARHNPARPVFVEGPFSL  
WLRNKCYYHILRADLLPPEEREVEETPEEWNLYYPMQLDLEYVRSGWDNYEFDINEV  
EEGPVFAMCMAGAHDQATMAKWIQGLQETNPTLAQIPVVFRLAGSTRELQTSSAGLEE  
PPLPEDHQEEDDNLQRQQGQS

SEQ ID No:114

MPSASCDTLLDDIEDIVSQEDSKPQDRHFVRKDVVPKVRRRRNTQKYLQEEENSPPSDS  
TIPGIQKIWIRTWGCSHNSDGEYMAGQLAAYGYKITENASDADLWLLNSCTVKNPAED  
HFRNSIKKAQEENKKIVLAGCVPQAQPRQDYLKGLSIIGVQQIDRVVEVVEETIKGHSVR  
LLGQKKDNGRRLGGARLDLPKIRKNPLIEIISISTGCLNACTYCKTKHARGNLASYPIDEL  
VDRAKQSFQEGVCEIWLTS EDTGAYGRDIGTNLPTLLWKLVEVIPEGAMLRLGMTNPPY  
ILEHLEEMAKILNHPRVYAFLHIPVQSASDSVLMEMKREYCVADFKRVVDLKEKVPGITI  
ATDIICGFPGETDQDFQETVKLVEEYKFPSLFINQFYPRPGTPAAKMEQVPAQVKKQRT  
KDLSRVFHSYSPYDHKIGERQQVLVTEESFDSKFYVAHNQFYEQVLVPKNPAFMGKMV  
EVDIYESGKHFMKGQPVSDAKVYTPSISKPLAKGEVSGLTKDFRNLGNQLSSGSHTS  
AASQCDSASSRMVLPMPRLHQDCALRMSVGLALLGLLFAFFVKVYN

SEQ ID No:115

MGGTTSTRRVTFEADENENITVVKGIRLSENVIDRMKESSPSGSKSQRYSGAYGASVS  
DEELKRRVAEELALEQAKKESEDQKRLKQAKELDRERAAANEQLTRAILRERICSEEER  
AKAKHLARQLEEKDRVLLKKQDAFYKEQLARLEERSSEFYRVTTTEQYQKAAEEVEAKFK  
RYESHPCADLQAKILQCYRENTHTLTKCSALATQYMHCNVNHAQSMLEKGG

SEQ ID No:116

MALAAARLLPQFLHSRSLPCGAVRLRTPAVAEVRLPSATLCYFCRCRLGLGAALFPRSAR  
 ALAASALPAQGSRWVPLSSPGLPAAFASFPACPQRSYSTEEKPQQHQKTKMIVLGFSN  
 PINWVRTRIKAFLIWAYFDKEFSITEFSEGAQKQAFHVSLLSQCKFDLLEELVAKEVLHA  
 LKEKVTSLPDNHKNALANIDEIVFTSTGDISIYYDEKGRKFVNILMCFWYLTSAIPSETL  
 RGASVFQVKLGNQNVETKQLLSASYEFQREFTQGVKPDWTIARIEHSLLE

SEQ ID No:117

MLLQQLRPHLEGCRNDIVSARPDEWLGRCLDATGVGCTGDHEGVHYSHLELSPGEPV  
 QEGDPHFERSALTAHPVRDPVHMYQLHKAFARAELETTYQEIQELQWEIQNTSHLAVDG  
 DRAAAWPVGIPAPSRPASRFEVLRWDYFTEQHAFSCADGSPRCPLRGADRADVADVL  
 GTALEELNRRYHPALRLQKQQLVNGYRRFDPARGMEYTLDLQLEALTPQGGRRPLTRR  
 VQLLRPLSRVEILVPYVTEASRLTVLLPLAAERDLAPGFLEAFATAALEPGDAAAALTL  
 LLLYEPRQAQRVAHADVFAPVKAHVAELERRFPGARVPWLSVQTAAPSPLRLMDLLSK  
 KHPLDTLFLLAGPDTVLTDFLNRCRMHAISGWQAFFPMHFQAFHFAVAPPQGPPE  
 LGRDTGRFDRQAASEACFYNSDYVAARGRLAAASEQEEELLESLDVYELFLHFSSLHVL  
 RAVEPALLQRYRAQTCSARLSEDLYHRCLQSVLEGLGSRTQLAMLLFEQEQQNST

SEQ ID No:118

MKLKLNKVFAYFLVSIAGLLYALVQLGQPCDCLPPLRAAAEQLRQKDLRISQLQAEARR  
 PPPAPAQPPEPEALPTIYVVTPTYARLVQKAELVRLSQTLSLVPRLHWLLVEDAEGPTPL  
 VSGLLAASGLLFTHLVLTTPKAQRLREGEPGWVHPRGVEQRNKALDWLRGRGGAVGG  
 EKDP PPPGTQGVVYFADDDNTYSRELSEEMRWTRGVSVPVGLVGGRLFEQGPVQD  
 GRVVGFTAWEPSRPFVDMAGFAVALPLLLDKPNAQFDSTAPRGHLESSLLSHLVDP  
 KDLEPRAANCTRVLVWHTRTKPKMKQEEQLQRQGRGSDPAIEV

SEQ ID No:119

MAAPRAGRAGWSLRAWRALGGIRWGRRPRLTPDLRALLTSGTSDPRARVTYGTPSL  
 WARLSVGVTEPRACLTSGTPGPRAQLTAVTPDTRTREASENSGTRSRAWLAVALGAG  
 GAVLLLLWGGGRGPPAVLAAPSPPPASPRSQYNFIADVVEKTAPAVVYIEILDRHPFLG  
 REVPISSNGSGFVVAADGLIVTNAHVADRRRVVRVRLLSGDTYEAVVTAVDPVADIATLRI  
 QTKEPLPTLPLGRSADVRRQGEFVAMGSPFALQNTITSGIVSSAQRPARDLGLPQTNVE  
 YIQTDAAIDFGNSGGPLVNLGGEVIGVNTMKVTAGISFAIPSDRLREFLHRGEKKNSSSGI

SGSQRRYIGVMMLTLSPSILAEQLREPSFPDVQHGVLIHKVILGSPAHRAGLRPGDVIL  
AIGEQMVQNAEDVYEAVRTQSQLAVQIRRGRETTLTYVTPEVTE

SEQ ID No:120

MTQLFLWEYGDHLHFGPNQRPAPCYDPCEAVLVESIPEGLDFPNASTGNPSTSQAWL  
LAGAHSSLDIASFYWTLTNNDHTHQEPSAQGGEEVLRQLQTLAPKGVNVRIAVSKPSG  
PQPQADLQALLQSGAQVRMVDQMQLTHGVLHTKFWVVDQTHFYLG SANMDWRS  
LTKVKELGVMYNCSCCLARDLT KIFEAYWFLGQAGSSIPSTWPRFYDTRYNQETPMEIC  
LNGTPALAYLASAPPPLCPSGRTPDLKALLNVVDNARSFIYVAVMNYLPTLEFSHPHR  
FWPAIDDGLRRATYERGVKVRLLISCWGHSEPSMRAFLLSLAALRDNHTHSDIQVKLFV  
VPADEAQARIPYARVNHNKYMVTERATYIGTSNWSGNYFTETAGTSLLVTQNGRGGLRS  
QLEAIFLRDWDSPIYHDLDT SADS VGNACRLL

SEQ ID No:121

RVYADAPAKLLLPPPAAWDLAVRLRGAEAAASERQVYSVTMKLLLLHPAFQSC  
LLLTLLGLWRTTPEAHASSLGAPISAASFLQDLIHYGEGDSLTLQQLKALLNHLDVGV  
GRGNVTQHVQGHRLNSTCFSSGDLFTA HNFSEQSRIGSSELQEF CPTILQQLDS  
RACTSENQEN.EENEQTEEGRPSAVEVWGYGLLCVTVISLCSLLGASVVPFMKKT  
FYKRLLLYFIALAIGTLYSNALFQLIPEAFGFNPLEDYYVSKSAVVFGFYLFFFT  
EKILKILLKQKNEHHHGHSHYASESLPSKKDQEEGVMEKLQNGDLDHMIPQHCS  
SEL DKGAPMVDEKVIVGSLSVQDLQASQSACYWLKGVRYSDIGTLAWMITLSDGL  
HNFIDGLAIGASFTVSVFQGISTSVAILCEEFPHELGD FVILLNAGMSIQQALFFN  
FLSACCCYLGLAFGILAGSHFSANWIFALAGGMFLYISLADMFP EMNEVCQEDERK  
GSILIPFIIQNLGLLTGFTIMVVLTMYSGQIQIG

SEQ ID No:122

MAAEWASRFWLWATLLIPAAVYEDQVGKFDWRQQYVGKVKFASLEFSPGSKKL  
VVA TEKNVIAALNSRTGEILWRHVDKGTAEGAVDAMLLHGQDVITVSNGGRIMRS  
WETNIGGLNWEITLDSGSFQALGLVGLQESVRYIAVLKKTTLALHHLSSGHLKWV  
EHLPESDSIHYQMVYSYGSGVWVWALGVVPF SHVNIVKFNVEDGEIVQQVRVSTP  
WLQHLSGACGVVDEAVLVCPDPSSRSLQTLALETWELRQIPLQSLDLEFGSGFQPRV  
LPTQPNPVDASRAQFFLHLSPSHYALLQYHYGTLSLLKNFPQTALVSFATTGEKT  
VAAMACRNEVQKSSSSSEDGSMGSFSEKSSSKDSLACFNQTYTINLYLVETGRRL  
LDTTITFSLEQSGTRPERLYIQVFLKKDDSVGYRALVQTEDHLLLFLQQLAGKVV  
LWSREESLAEVVCLEMVDLPLTGAQAELEGEFGKKADGLLGMFLKRLSSQLILLQ  
AWTSHLWKMFYDARKPRSQIKNEINIDTLARDEF

NLQKMMVMVTASGKLFGISSSGTILWKQYLPNVKPDSSFKLMVQRTTAHFPHPPQCT  
 LLVKDKESGMSSLYVFNPIFGKWSQVAPPVLKRPILQSLLLPVMDQDYAKVLLLLIDDEYK  
 VTAFPATRNVLRLHELAPSIFFYLVDAEQGRLCGYRLRKDLTTESWELTIPPEVQRIV  
 KVKGKRSEHVHSQGRVMGDRSVLYKSLNPNLLAVVTESTDAHHERTFIGIFLIDGVTG  
 RIIHSSVQKKAKGPVHIVHSENWVYQYWNTKARRNEFTVLELYEGTEQYNATAFSSLD  
 RPQLPQVLQQSYIFPSSISAMEATITERGITSRHLLIGLPSGAILSLPKALLDPRRPEIPTE  
 QSREENLIPYSPDVQIHAERFINYNQTVSRMRGIYTAPSGLESTCLVVAYGLDIYQTRVY  
 PSKQFDVLKDDYDYVLISSVLFGLVFATMITKRLAQVKLLNRAWR

SEQ ID No:123

MAKVSELYDVTWEEMRDKMRKWREENSERNSEQIVEVGEELINEYASKLGDDIWIIIEQV  
 MIAALDYGRDDLALFCLQELRRQFPGSHRVKRLTGMRFEAMERYDDAIQLYDRILQEDP  
 TNTAARKRKIAIRKAQGNVEAIRELNEYLEQFVGQDEAWHELAELYINEHDYAKAAFCCL  
 EELMMTNPHNHLYCQQYAEVKYTQGGLENLELSRKYFAQALKLNNRNMALFGLYMS  
 ASHIASNPKASAKTKKDNMKYASWAASQINRAYQFAGRSKKETKYSCLKAVEDMLETQI  
 TQS

SEQ ID No:124

LERRWRRRREAGAGAEAAAGSARPLGRQAAAARGSSPEAGAAAMAESIIIRVQSPDGV  
 KRITATKRETAATFLKKVAKEFGFQNGFSVYINRNKTGEITASSNKSLLKIKHGDLLF  
 LFPSSLAGPSSEMETSVPFGFKVFGAPNVVEDEIDQYLSKQDGKIYRSRDPQLCRHGPL  
 GKCVHCVPLEPFDELYLNHLEPPVKHMSFHAYIRKLTGGADKGKFVALENISCKIKSGC  
 EGHLPWPNGICTKCQPSAITLNRQKYRHVDNIMFENHTVADRFLDFWRKTGNQHFHYL  
 YGRYTEHKDIPLGIRAEVAAIYEPPQIGTQNSLELLEDPKAEVVDEIAAKLGLRKVGWIFT  
 DLVSEDTRKGTVRYSRNKDTYFLSSEECITAGDFQNKHPNMCRLSPDGHFGSKFVTAV  
 ATGGPDNQVHFEGYQVSNQCMALVRDECLLPCKDAPELGYAKESSEQYVPDVFYKD  
 VDKFGNEITQLARPLPVEYLIIDITTFPKDPVYTFSSISQNPFPPIENRDVLGETQDFHSLAT  
 YLSQNTSSVFLDTISDFHLLLFLVTNEVMPLQDSISLLEAVRTRNEELAQTWKRSEQWA  
 TIEQLCSEYPHPLPRHPVAGAGEQPTLHSSPLPVVPWIPHPAASWQVPSAMQRVETRP  
 PCQARGRLR

SEQ ID No:125

MWSIGAGALGAAALALLANTDVFLSKPQKALEYLEDIDLKLEKEPRTFKAKELWEKN  
 GAVIMAVRRPGCFLCREEAADLSSLKSMQLDQLGVPLYAVVKEHIRTEVKDFQPYFKGEI

FLDEKKKFYGPQRRKMMFMGFIRLGWYNFFRAWNGGFSGNLEGEFGFILGGVFVVGSGKQGILLEHREKEFGDKVNLLSVLEAAKMIKPQTLASEKK

SEQ ID No:126

MASGSNWLSGVNVVLVMAYGSLVFVLLFIFVKRQIMRFAMKSRRGPHVPVGHNAPKDL  
KEEIDIRLSRVQDIKYEPQLLADDDARLLQLETQGNQSCYNYLYRMKALDAIRTSEIPFHS  
EGRHPRSLMGKNFRSYLLDLRNTSTPFKGVKALIDTLLDGYETARYGTGVFGQNEYL  
RYQEALSELATAVKARIGSSQRHHQSAAKDLTQSPEVSPTTIQVTYLPSSQKSKRAKHF  
LELKSFKDNYNTLESTL

SEQ ID No:127

MSGCGLFLRTTAAARACRGLVVSTANRRLLRTSPPVRAFAKELFLGKIKKKEVFPFPEV  
SQDELNEINQFLGPVEKFFTEEVDSRKIDQEGKIPDETLEKLKSLGLFGLQVP E E Y G G L G  
FSNTMYSRLGEIISMDGSITVTAAHQAIGLKGILAGTEEQKAKYLPKLASGEHIAAFCLT  
EPASGSDAASIRSRTLSEDKKH Y I L N G S K V W I T N G G L A N I F T V F A K T E V V D S D G S V K D K  
ITAFIVERDFGGVTNGKPEDKLGIRGSNTCEVHFENTKIPVENILGEVGDGFKVAMNILNS  
GRFSMGSVVAGLLKRLIEMTAEYACTRKQFNKRLSEFGLIQEKFALMAQKAYVMESMT  
YLTAGMLDQPGFPDCSIEAAMVKVFSSEA W Q C V S E A L Q I L G G L G Y T R D Y P Y E R I L R D T  
RILLIFEGTNEILRMYIALTGLQHAGRILTTRIHELKQAKVSTVMDTVGRRLRDSLGR TV D L  
GLTGNHGVVHPSLADSANKFEENTYCFGR TV E T L L L R F G K T I M E E Q L V L K R V A N I L I N L Y  
GMTAVLSRASRSIRIGLRNHDHEVLLANTFCVEAYLQNLFSLSQLDKYAPENLDEQIKKV  
SQQILEKRAYICAHPLDRTC

SEQ ID No:128

MPSAKQRGSKGGHGAASPSEKGAHPSGGADDVAKKPPPAPQQPPPPAPHPQQHPQ  
QHPQNQAHGKGGH R G G G G G G K S S S S S S A S A A A A A A A S S S S A S C S R R L G R A L N F L F  
YLALVAAA F S G W C V H H V L E E V Q Q V R R S H Q D F S R Q R E E L G Q G L Q G V E Q K V Q S L Q A T F  
GTFESILRSSQHKQDLTEKAVKQGESEVSRISEVLQKLQNEILKDLSDGIHVVKDARERD  
FTSLENTVEERLTETKSINDNIAIFTEVQKRSQKEINDMKAKVASLEESEGNKQDLKALK  
EAVKEIQTSAKSREWDMEALRSTLQTMESDIYTEVRELVS L K Q E Q Q A F K E A A D T E R L A L  
QALTEKLLRSEESVSRLPEEIRRLEEELRQLKSDSHGPKEDGGFRHSEAFEALQQKSQ  
GLDSRLQHVEDGVL SM Q V A S A R Q T E S L E S L L S K S Q E H E Q R L A A L Q G R L E G L G S S E A D  
QDGLASTVRSLGETQLVLYGDVEELKRSVGELPSTVESLQKVQE Q V H T L L S Q D Q A Q A A

RLPPQDFDLRLSSLDNLKASVSQVEADLKMLRTAVDSLVAYSVKIETNENNLESAKGLL  
DDLNRNDLDRLFVKVEKIHKEV

SEQ ID No:129

MFRNQYDNDVTWVSPQGRIHQIEYAMEAVKQGSATVGLKSKTHAVLVALKRAQSELAA  
HQKKILHVDNHIGISIAGLTADARLLCNFMRQECLDSRFVFDRLPVSRLVSLIGSKTQIP  
TQRYGRRPYGVGLLIAGYDDMGPHIFQTCPSANYFDCRAMSIGARSQSARTYLERHMS  
EFMECNLNELVKHGLRALRETLPAEQDLTTKNVSIGIVGKDLEFTIYDDDDVSPFLEGLE  
ERPQRKAQPAQPADEPAEKADDEPMEH

SEQ ID No:130

SSIGTGYDLSASTFSPDGRVFQVEYAMKAVENTSSTAIGIRCKDGVVFGVEKLVLSKLYEE  
GSNKRLFNVDRHVGMVAVAGLLADARSLADIAREEASNFRSNFGYNIPLKHLADRVAMY  
VHAYTLYSAVRPFGCSFMLGSYSVNDGAQLYMIDPSGVSYGYWGCAIGKARQAAKTEI  
EKLQMKEMTCRDIVKEVAKIYIVHDEVKDKAFELELSWVGELTNGRHEIVPKDIREEAEK  
YAKESLKEEDESDDDNM

SEQ ID No:131

MSRRYDSRTTIFSPTEGRLYQVEYAMEAIGHAGTCLGILANDGVLLAAERRNIHKLLDEVF  
FSEKIYKLNEDMACSVAGITSDANVLTNELRLIAQRYLLQYQEPIPCQLVTALCDIKQAY  
TQFGGKRPFVGSLLYIGWDKHYGFQLYQSDPSGNYGGWKATCIGNNSAAAVSMLKQD  
YKEGEMTLKSALALAIKVLNKTMDVSKLSAEKVEIATLTRENGKTVIRVLKQKEVEQLIKK  
HEEEEEAKAEREKKEKEQKEKDK

SEQ ID No:132

MSRGSSAGFDRHITIFSPTEGRLYQVEYAFKAINQGGLTSVAVRGKDCAVIVTQKKVPDK  
LLDSSTVTHLFKITENIGCVMTGMTADSRSQVQRARYEAANWKYKYGYEIPVDMCKRI  
ADISQVYTQNAEMRPLGCCMILIGIDEEQGPQVYKCDPAGYYCGFKATAAGVKQTESTS  
FLEKKVKKKFDWTFEQTVETAITCLSTVLSIDFKPSEIEVGWVTVENPKFRILTEAEIDAHL  
VALAERD

SEQ ID No:133

MLSSTAMYSAPGRDLGMEPHRAAGPLQLRFSPYVFNGGTILAIAGEDFAIVASDTRLSE  
GFSIHTRDSPKCYKLTDKTVIGCSGFHGDCLTLTKIIEARLKMYSNNKAMTTGAIAAM

LSTILYSRRFFPYVYVNIIGGLDEEGKGAVYSFDPVGSYQRDSFKAGGSASAMLQPLLD  
NQVGFKNMQNVEHVPLSLDRAMRLVKDVFISAAERDVYTG DALRICIVTKEGIREETVSL  
RKD

SEQ ID No:134

MEYLIGIQGPDYVLVASDRVAASNIVQMKDDHDKMFKMSEKILLLCVGEAGDTVQFAEYI  
QKNVQLYKMRNGYELSPTAAANFTRRN LADCLRSRTPYHVNLLLAGYDEHEGPALYYM  
DYLAALAKAPFAAHGYGAFLTLSILD RYYP TISRERAVELLRKCLEELQKRFILNLPTFSV  
RIIDKNGIHDLDNISFPKQGS

SEQ ID No:135

MSIMSYNGGAVMAMKGKNCVAIAADRRFGIQAQMVTTDFQKIFPMGDRLYIGLAGLATD  
VQTV AQRLKFRNLNLYELKEGRQIKPYTLM SMVANLLYEKRF GPPYTEPVIAGLDPKTFKP  
FICSLDLIGCPMVTDDFV VSGTCAEQMYGMCESLWEPNMDPDHLFETISQAMLNAVDR  
DAVSGMGVIVHIEKDKITRTLKARM D

SEQ ID No:136

MEAFLGSRSGLWAGGPAPGQFYRIPSTPDSFMDPASALYRGPITRTQNPMVTGTSVLG  
VKFEGGVVIAADMLGSYGLARFRNISRIMRVNNSTMLGASGDYADFQYLKQVLGQMVI  
DEELLGDGHSYSPRAIHSWLTRAMYSRRSKMNPLWNTMVIGGYADGESFLGYVDMLG  
VAYEAPSLATGYGAYLAQPLLREVLEKQPVLSQTEARDLVERCMRVLYYRDARSYNRF  
QTATVTEKGVEIEGPLSTETNWDIAHMISGFE

SEQ ID No:137

MLHGTTTLAFKFRHGVIVAADSRATAGAYIASQTVKKVIEINPYLLGTMAGGAADCSFWE  
RLLARQCRIYELRNKERISVAAASKLLANMVYQYKGMGLSMGTMICGWDKRGPGLYYV  
DSEGNRISGATFSVSGSVYAYGVMDRGYSYDLEVEQAYDLARRAIYQATYRDAYS GG  
AVNLYHVREDGWIRVSSDNVADLHEKYSGSTP

SEQ ID No:138

MAATLLAARGAGPAPAWGPEAFTP DWESREVSTGTTIMAVQFDGGVVLGADSRTTTG  
SYIANRVTDKLTPIHDRIFCCRS GSAADTQAVADAVTYQLGFHSIELNEPPLVHTAASLFK  
EMCYRYREDLMAGIIIAGWDPQEGGQVYSVPMGGMMVRQSFAIGSGSSYIYGYVDA

TYREGMTKEECLQFTANALALAMERDGSSGGVIRLAAIAESGVERQVLLGDQIPKFAVA  
TLPPA

SEQ ID No:139

MGQSQSGGHGPGGGKKDDKDKKKKYEPVPTRVGKKKKKTGPDAAASKLPLVTPHT  
QCRLKLLKLERIKDYLLMEEEFIRNQEQMKNPLEEKQEEERSKVDDLRGTPMSVGTLEEII  
DDNHAIVSTSVGSEHYVSILSFVDKDLLEPGCSVLLNHKVHAVIGVLMDDTDPLVTVMKV  
EKAPQETYADIGGLDNQIQEIKESVELPLTHPEYYEEMGIKPPKGVILYGPPGTGKTLLAK  
AVANQTSATFLRVVGSELIQKYLGDGPKLVRELFVAAEEHAPSIVFIDEIDAIGTKRYDSN  
SGGEREIQRTMLELLNQLDGFDSRGDVKVIMATNRIETLDPALIRPGRIDRKIEFPLPDEK  
TKKRIFIHTSRMTLADDVTLDDLIMAKDDLSGADIKACTEAGLMALRERRMKVTNEDF  
KKSKENVLYKKQEGTPEGLYL

SEQ ID No:140

MPDYLGAQQRKTKEDKDDKPIRALDEGDIALLKTYGQSTYSRQIKQVEDDIQQLLKIN  
ELTGIKESDTGLAPPALWDLAADKQTLQSEQPLQVARCTKIINADSEDPKYIINVKQFAKF  
VVDLSQQVAPTDIEEGMRVGVDRNKYQIHIPLPPKIDPTVTMMQVEEKPDVTYSQVGGC  
KEQIEKLREVVETPLLHPERFVNGLIEPPKGVLLFGPPGTGKTLCAVANRTDACFIRVI  
GSELVQKYVGEGARMVRELFEMARTKKAELIFFDEIDAIGGARFDDGAGGDNEVQRTM  
LELINQLDGFDPGRNIKVLNATNRPDTLDPALMRPGRIDRKIEFSLPDLEGRTHIFKI HAR  
SMSVERDIRFELLARLCPNSTGAEIRSVCTEAGMFAIRARRKATEKDFLEAVNKVKSIA  
KFSATPRYMTYN

SEQ ID No:141

MNLLPNIESPVTRQEKMATVWDEAEQDGIGEEVLKMSTEEIIQRTRLLDSEIKIMKSEVL  
RVTHELQAMKDKIKENSEKIKVNKTLPYLVSNVIELLDVDPNDQEEDGANIDLDSQRKKG  
CAVIKTSTRQTYFLPVIGLVDAEKLKPGDLVGVNKDSYLILETLPTHEYDSRVKAMEVDER  
PTEQYSDIGGLDKQIQELVEAIVLPMNHKEKFENLGIQPPKGVLMYGPPTGKTLLARAC  
AAQTKATFLKLAGPQLVQMFIDGAKLVRFDAFALAKEKAPSIIFIDELDAIGTKRFDSEKA  
GDREVQRTMLELLNQLDGFQPNQVQVIAATNRVDILDPALLRSGRLDRKIEFPMPNEE  
ARARIMQIHSRKMNVSQDVNYEELARCTDDFNGAQCKAVCVEAGMIALRRGATELTHE  
DYMEGILEVQAKKANLQYYA

SEQ ID No:142

MEEIGILVEKAQDEIPALSVSRPQTGLSFLGPEPEDLEDLYSRYKKLQQELEFLEVQEEYI  
 KDEQKNLKKEFLLHAQEEVKRIQSIPLVIGQFLEAVDQNTAIVGSTTGSNYYVRILSTIDRE  
 LLKPNASVALHKHSNALVDVLPPEADSSIMMLTSDQKPDV MYADIGGMDIQKQEVREAV  
 ELPLTHFELYKQIGIDPPRGVLMYGPPGCGKTMLAKAVAHHTTAAFIRVVGSEFVQKYL  
 GEGPRMVRDVFR LAKENAPAIIFIDEIDAIATKRFDAQTGADREVQRILLELLNQMDGFD  
 QNVNVKVIMATNRADTLDPALLRPGR LDRKIEFPLPDRRQKRLIFSTITSKMNLSEEVDL  
 EDYVARPDKISGADINSICQESGMLAVRENRYIVLAKDFEKAYKTVIKKDEQEHEFYK

SEQ ID No:143

MALDGPEQMELEEGKAGSGLRQYYLSKIEELQLIVNDKSQNLRRRLQAQRNELNAKVRL  
 REELQLLQEQGSYVGEVVRAMDKKKVLVKVHPEGKFVVDVDKNIDINDVTPNCRVALR  
 NDSYTLHKILPNKVDPLVSLMMVEKVPDSTYEMIGGLDKQIKEIKEVIELPVKHPELFEAL  
 GIAQPKGVLLYGPPGTGKTLLARAVAHHTDCTFIRVSGSELVQKFIGEGARMVRELFVM  
 AREHAPSIIFMDEIDSIGSSRLEGGSGGDSEVQRTMLELLNQLDGFEATKNIKVIMATNRI  
 DILDSALLRPGRIDRKIEFPPPNEEARLDILKIHSRKMNLTRGINLRKIAELMPGASGAEVK  
 GVCTEAGMYALRERRVHVTQEDFEMAVAKVMQKDSEKNMSIKKLWK

SEQ ID No:144

MADPRDKALQDYRKKLLEHKEIDGRLKELREQLKELTKQYEKSENDLKALQSVGQIVGE  
 VLKQLTEEFKIVKATNGPRYVVGCRRLDKSKLKPGRVALDMTTLTIMRYLPREVDPL  
 VYNMSHEDPGNVSYSEIGGLSEQIRELREVIPLTNPELFQRVGIIPPKGCLLYGPPGT  
 GKTLLARAVASQLDCNFLKVSSSIVDKYIGESARLIREMFNYARDHQPCIIIFMDEIDAIG  
 GRRFSEGTSADREIQRTLME LLNQMDGFDTLHRVKMIMATNRPDTLDPALLRPGR LDR  
 KIHIDLPNEQARLDILKIHAGPITKHGEIDYEAIVKLSGDFNGADLRNVCTEAGMFAIRADH  
 DFVVQEDFMKAVRKVADSKKLESKLDYKPV

SEQ ID No:145

MITSAAGIISLLDEDEPQLKEFALHKLNAVVNDFWAEISESVDKIEVLYEDEGFRSRQFAA  
 LVASKVIFYHLGAFEE SLNYALGARDLFNVNDNSEYVETIIAKCIDHYTKQCVENADLPEG  
 EKKPIDQRLEGIVNKM FQRCLDDHKYKQAIGIALETRRLDVFEKTILESNDVPGMLAYSL  
 KLCMSLMQNKQFRNKVLRVLVKIYMNLEKPDFINVCQCLIFLDDPQAVSDILEKL VKEDN  
 LLMAYQICFDLYESASQQFLSSVIQNLRTVGTPIASVPGSTNTGTVPGSEKDSDSMETE  
 EKTSSAFVGKTPEASPEPKDQTLKMIKILSGEMAIELHLQFLIRNNNTDLMILKNTKDAVR  
 NSVCHTATVIANSFMHCGTTSQQLRDNLEWLARATN WAKFTATASLGVIHKGHEKEAL

QLMATYLPKDTSPGSAYQEGGGLYALGLIHANHGDDIIDYLLNQLKNASNDIVRHGSSL  
 GLGLAAMGTARQDVYDLLKTNLYQDDAVTGEAAGLALGLVMLGSKNAQAIEDMVGYAQ  
 ETQHEKILRGLAVGIALVMYGRMEEADALIESLCRDKDPILRRSGMYTVAMAYCGSGNN  
 KAIRRLHVAVSDVNDDVRSAAVESLGFILFRTPEQCPSVVSLLSESYNPHVRYGAAMA  
 LGICCAGTGNKEAINLLEPMTNDPVNYVRQGALIASALIMIQQTEITCPKVNQFRQLYSKV  
 INDKHDDVMAKFGAILAQGILDAGGHNVTSISLQSRTGHTHMPSVVGVLVFTQFWFWFPL  
 SHFLSLAYTPTCVIGLNKDLKMPKVQYKSNCKPSTFAYPAPLEVPEKEKEKEKVSTAVLSI  
 TAKAKKKEKEKEKKEEEKMEVDEAEKKEEKEKKKEPEPNFQLLDNPARVMPAQLKVL  
 T  
 MPETCRYQPFKPLSIGGIILKDTSEDIELVEPVAAHGPKIEEEEQEPEPPEPFEYIDD

SEQ ID No:146

MAAAVVEFQRAQSLLSTDREASIDILHSIVKRDIQENDEEAVQVKEQSILELGSLLAKTG  
 QAAELGGLLKYPFLNSISKAKAARLVRSLDLFLDMEAATGQEVELCLECIEWAKSEK  
 RTFLRQALEARLVSLYFDTKRYQEALHLGSQLLRELKKMDDKALLVEVQLLESKTYHAL  
 SNLPKARAALTSARTTANAIYCPPKLQATLDMQSGIIHAAEEKDWKTAYSIFYEAFEGYD  
 SIDSPKAITSCLKYMLLCKIMLNTPEDVQALVSGKLALRYAGRQTEALKCVAQASKNRSLA  
 DFEKALTDYRAELRDDPIISTHLAKLYDNLLEQNLIRVIEPFSRVQIEHISLIKLSKADVER  
 KLSQMILDKKFHGILDQGEVLIIFDEPPVDKTYEAALETIQNMSKVVDLSYNKAKKLT

SEQ ID No:147

MADGGSERADGRIVKMEVDYSATVDQRLPECAKLAKEGRLQEVIETLLSLEKQTRTASD  
 MVSTSRILVAVVKMCYEAKWDLLENIMLLSKRRSQLKQAVAKMVQQCCTYVEEITDL  
 PIKRLRIDTLRMVTEGKIYVEIERARLTKLATIKEQNGDVKEAASILQELQVETYGSMEKK  
 ERVEFILEQMRLCLAVKDYIRTQIISKKINTKFFQEENTEKLKLYYNLMIQLDQHEGSYLS  
 ICKHYRAIYDTPCQAESEKWQQALKSVVLYVILAPFDNEQSDLVHRISGDKKLEEIPKYK  
 DLLKLFTTMELMRWSTLVEDYGMELRKSLESPATDVFGSTEEGEKRWKDLKNRVVE  
 HNIRIMAKYYTRITMKRMAQLLDLSVDESEAFSLNLVVKNTIFAKVDRLAGIINFQRPKDP  
 NNLLNDWSQKLNSLMSLVNKTTHLIAKEEMIHNLQ

SEQ ID No:148

MKDVPGLQSQNSGPGQPAVWHREELYTKKLWHQLTLQVLDVQDPCFAQGDGLI  
 KLYENFISEFEHRVNPLSLVEIILHVVRQMTDPNVALTFLEKTRKVKSSDEAVILCKTAIG  
 ALKLNIGDLQVTKETIEDVEEMLNNLPGVTSVHSRFDLSSKYYQTIGNHASYYKDALARF  
 LGCVDIKDLPVSEQQERAFTLGLAGLLGEGVFNFGEMLMHPVLESRLNTRQWLIDTLY

AFNSGNVERFQTLKTAWGQQPDLAANEAQLLRKIQLLCLMEMTFTRPANHRQLTFEEIA  
KSAKITVNEVELLMKALSVGLVKGSIDEVDKRVHMTWVQPRVLDLQQIKGMKDRLEF  
WCTDVKSMEMLVEHQAHDILT

SEQ ID No:149

MEEGGRDKAPVQPQQSPAAAPGGTDEKPSGKERRDAGDKDKEQELSEEDKQLQDEL  
EMLVERLGEKDTSLYRPALEELRRQIRSSSTTSMTSVPKPLKFLRPHYGKLKEIYENMAP  
GENKRFAADIISVLAMTMSGERECLKYRLVGSQEELASWGHEYVRHLAGEVAKEWQEL  
DDAEKVQREPLTLVKEIVPYNMAHNAEHEACDLLMEIEQVDMLEKDIDENAYAKVCLYL  
TSCVNYVPEPENSALLRCALGVFRKFSRFEALRLALMLNDMELVEDIFTSCKD VVQK  
QMAFMLGRHGVFLELSEEDVEEYEDLTEIMSNVQLNSNFLALARELDIMEPKVPDDIYKT  
HLENNRFGGSGSQVDSARMNLASSFVNGFVNAAFQGDKLLTDDGNKWLYKNKDHGM  
LSAAASLGMILLWDVDGGLTQIDKYLYSSEDIKSGALLACGIVNSGVRNECDPALALLS  
DYVLHNSNTMRLGSIFGLGLAYAGSNREDVLTLLLPVMGDSKSSMEVAGVTALACGMIA  
VGSCNGDVTSTILQTIMEKSETELKDTYARWLPLGLGLNHLGKGAEIAAILAALEVSEPF  
RSFANTLVDVCAYAGSGNVLKVQQLLHICSEHFDSKEKEEDKDKKEKKDKDKKEAPAD  
MGAHQGVAVLGIALIAMGEEIGAEMALRTFGHLLRYGEPTLRRAVPLALALISVSNPRLNI  
LDTLSKFSDHADPEVSYNSIFAMGMVSGTNNARLAAMLRLQAQYHAKDPNNLFMVRL  
AQGLTHLGKGTTLCPYHSDRQLMSQVAVAGLLTVLVSFVDVRNIILGKSHYVLYGLVAA  
MQPRMLVTFDEELRPLPVSVRVGQAVDVVGQAGKPKTITGFQTHHTPVLLAHGERAEL  
ATEEFLPVTPILEGFVILRKNPNYDL

SEQ ID No:150

MKQEGSARRRGADKAKPPPGGGEQEPPPPAPQDVEMKEEAATGGGSTGEADGKTA  
AAAAEHSQRELDTVTLEDIKEHVKQLEKAVSGKEPRFVLRALRMLPSTSRRLNHVLYK  
AVQGFFTSNNATRDFLLPFLEEPMDTEADLQFRPRTGKAASTPLLPEVEAYLQLLVVIFM  
MNSKRYKEAQKISDDL MQKISTQNRALDLVAAKCYYYHARVYEFDKLDVVRSLHAR  
LRTATLRHDADGQATLLNLLLRNYLHYSLYDQAEKLVSKSVFPEQANNNEWARYLYT  
GRIKAIQLEYSEARRTMTNALRKAPQHTAVGFKQTVHKLLIVVELLLGEIPDRLQFRQPSL  
KRSLMPYFLLTQAVRTGNLAKFNQVLDQFGEKFQADGTYTLIIRLRHNVIKTGVRMISLS  
YSRISLADIAQKLQLDSPEDAEIFIVAKAIRDGVIEASINHEKGYVQSKEMIDIYSTREPQLA  
FHQRISFCLDIHNMSVKAMRFPPKSYNKDLESAEERREREQQDLEFAKEMAEDDDDSF  
P

SEQ ID No:151

MVLESTMVCVDNSEYMRNGDFLPTRLQAQQDAVNIVCHSKTRSNPENNVGLITLANDC  
EVLTTLTPTDGRILSKLHTVQPKGKITFCTGIRVAHLALKHRQGKNHKMRIIAFVGSPVED  
NEKDLVKLAKRLKKEKVNVDIINFGEEEVNTEKLTAFVNTLNGKDGTGSHLVTVPGPSL  
ADALISSPILAGEGGAMLGLGASDFEFGVDPSADPELALALRVSMEEQRQRQEEEEARR  
AAAASAAEAGIATTGTEDSDDALLKMTISQQEFGRGTGLPDLSSMTEEEQIAYAMQMSLQ  
GAIEFGQAESADIDASSAMDTSEPAKEEDDYDVMQDPEFLQSVLENLPGVDPNNEAIRN  
AMGSLASQATKDGGKKDKKEEDKK

SEQ ID No:152

MLTFMASDSEEEVCDERTSLMSAESPTPRSCQEGRQGPEDGENTAQWRSQENEEEDG  
EEDPDRYVCSGVPGRPPGLEEEELTKYGAKHVIMLFVPVTLCMIVVATIKSVRFYTEKN  
GQLIYTPFTEDTPSVGQRLNNSVLNLTIMISVIVVMTIFLVVLYKYRCYKFIHGWLMSSLM  
LLFLFTYIYLGEVLKTYNVAMDYPTLLLTWNFGAVGMVCIHWKGPLVLQQAYLIMISAL  
MALVFIKYLPEWSAWVILGAISVYDLVAVLCPKGPLRMLVETAQERNEPIFPALIYSSAMV  
WTVGMAKLDPSSQGALQLPYDPEMEEDSYDSFGEPSYPEVFEPPLTGYPGEELEEEE  
ERGVKLGLGDFIFYSVLVGKAAATGSGDWNTTLACFVAILIGLCLTLLLLAVFKKALPALPI  
SITFGLIFYFSTDNLVRPFMDTLASHQLYI

SEQ ID No:153

MAAKVFESIGKFGLALAVAGGVVNSALYNVDAGHRAVIFDRFRGVQDIVVGEGTHFLIP  
WVQKPIIFDCRSRPRNPVITGSKDLQNVNITLRILFRPVASQLPRIFTSIGEDYDERVLPS  
ITTEILKSVMARFDAGELITQRELVSQRVSDDLTERAATFGLILDDVSLTHLTFGKEFTEAV  
EAKQVAQQAERARFVVEKAEQQKKAIIISAEGDSKAAELIANSLATAGDGLIELRKLEA  
AEDIAYQLSRNRNITYLPAGQSVLLQLPQ

SEQ ID No:154

MSGGPLSLPLALSPPRLLLLLLLLSLLPVARASEAEHRLFERLFEDYNEIIRPVANVSDPVII  
HFEVSMSQLVKVDEVNQIMETNLWLKQIWNKYKLKWNPSDYGGAEFMRVPAQKIWKP  
DIVLYNNAVGFQVDDKTKALLKYTG EVTWIPPAIFKSSCKIDVTYFPFDYQNCTMKFGS  
WSYDKAKIDLVLIGSSMNLKDYWESGEWAIKAPGYKHDIKYNCCIEIYPDITYSLYIRRL  
PLFYTINLIIPCLLISFLTVLVLYLPSCGKVTLCISVLLSLTVFLLVITETIPSTSLVIPLIGEY  
LLFTMIFVTLISIVITVFLNVHYRTPTTHTMPSWVKTVFLNLLPRVMFMTRPTSNEGNAQ  
KPRPLYGAELSNLNCFSRAESKGCKEGYPCQDGMCGYCHHRIKISNFSANLTRSSSS

ESVDAVLSLSALSPEIKEAIQSVKYIAENMKAQNEAKEEQKAQEIQQLKRKEKSTETSDQ  
EPGL

SEQ ID No:155

MPAHLQDDISSYTTTTTITAPPSRVLQNGGDKLETMPPLYLEDDIRPDIKDDIYDPTYKD  
KEGPSKVEYVWRNIILMSLLHLGALYGITLIPTCKFYTWLWGVFYYFVSALGITAGAHRL  
WSHRYSYKARLPLRLFLIIANTMAFQNDVYEWARHDRAHHKFSETHADPHNSRRGFFFFS  
HVGWLLVRKHPAVKEKGSTLDLSLEAEKLVMFQRRYYKPGLLMMCFILPTLVPWYFW  
GETFQNSVFVATFLRYAVVLNATWLVNSAAHLFGYRPHYDKNISPRENILVSLGAVGEGF  
HNYHHSFPYDYSASEYRWHINFTTFFIDCMAALGLAYDRKKVSKAAILARIKRTGDGNYK  
SG

SEQ ID No:156

MTSIHFVVHPLPGTEDQLNDRLREVSEKLNKYNLNSHPPLNVLEQATIKQCVVGPNHAA  
FLLEDGRVCRIGFSVQPDRLLELGPNDNDGSKLNSNSGAGRTSRPGRTSDSPWFLSG  
SETLGRLAGNTLGSRWSSGVGGSGGGSSGRSSAGARDSRRQTRVIRTGRDRGSGLL  
GSQPQPVIPASVIPEELISQAQVVLQGKSRSVIIRELQRTNLDVNLAVNNLLSRDDEDGD  
DGDDTASESYLPGEDLMSLLDADIHSAHPSVIIDADAMFSEDISYFGYPSFRRSSLRLG  
SSRVLLPLERDSELLRERESVLRLRERRWLDGASFDNERGSTSKEGEPNLDKKNTPV  
QSPVSLGEDLQWWPDKDGTKFICIGALYSELLAVSSKGELYQWKWSESEPYRNAQNP  
SLHHPRATFLGLTNEKIVLLSANSIRATVATENNKVATWVDETLSSVASKLEHTAQTYSE  
LQGERIVSLHCCALYTCAQLENSLYWWGVVPFSQRKKMLEKARAKNKKPKSSAGISSM  
PNITVGTQVCLRNPLYHAGAVAFSISAGIPKVGVLMEVWNMNDSCRFLRSPESLKN  
MEKASKTTEAKPESKQEPVKTEMGPPSPASTCSDASSIASSASMPYKRRRSTPAPKE  
EEKVNEEQWSLREVVFVEDVKNPVGKVLKVDGAYVAVKFPGTSSNTNCQNSSGPDA  
DPSSLLQDCRLLRIDELQVVKTGTPKVPDCFQRTPKKLCIPEKTEILAVNVDSKGVHAV  
LKTGNWVRYCIFDLATGKAEQENNFPTSSIAFLGQNERNVAIFTAGQESPIILRDGNGTIY  
PMAKDCMGGIRDPDWLDLPPISSLGMGVHSLINLPANSTIKKKA AVIIMAVEKQTLMQHIL  
RCDYEACRQYLMNLEQAVVLEQNLQMLQTFISHRCGDNRNILHACVSVCFPTS NKETK  
EEEEAERSENRTFAERLSAVEAIAANAISVVSSNGPGNRAGSSSSSRSLRLREMMRRSLR  
AAGLGRHEAGASSSDHQDPVSPPIAPPSWVPDPPAMD PDGDIDFILAPAVGSLTTAATG  
TGQGPSTSTIPGPSTEPSVVESKDRKANAHFILKLLCDSVVLQPYLRELLSAKDARGMT  
PFMSAVSGRAYPAAITILETAQKIAKAEISSSEKEEDVFMGMVCPSGTNPDDSPLYVLCC  
NDTCSFTWTGAEHINQDIFECRTCGLLESLCCCTECARVCHKGHDCKLKRTSPTAYCD

CWEKCKCKTLIAGQKSARLDLLYRLLTATNLVTL PNSRGEHLLLFLVQTVARQTVEHCQ  
 YRPPRIREDNRNKTASPEDSDMPDHDLEPPRF AQLALERV LQDWNALKSMIMFGSQEN  
 KDPLSASSRIGHLLPEEQVYLNQQSGTIRLDCFTHCLIVKCTADILLDTLLGTLVKELQN  
 KYTPGRREEAIAVTMRFLRSVARVFVILSVEMASSKKKNNFIPQPIGKCKRVFQALLPYA  
 VEELCNVAESLIVPVRMGIARPTAPFTLASTSIDAMQGSEELFSVEPLPPRPSSDQSSSS  
 SQSQSSSYIIRNPQQRRISQSQPVRGRDEEQDDIVSADVEEVEVVEGVAGEEDHHDEQE  
 EHGEENAEAEQGQHDEHDEDGSDMELDLLAAAE TESDSSENHNSNQDNASGRRSVVTAA  
 TAGSEAGASSVPAFFSEDDSQSNDSSSDSSSSQSDDIEQETFMLDEPLERTTNSSHA  
 NGAAQAPRSMQWAVRNTQHQR AASTAP SSTSTPAASSAGLIYIDPSNLRRTGTISTSA  
 AAAAALEASNASSYLTSASSLARAYSIVIRQISDLMGLIPKYNHLVYSQIPAAVKLT YQDA  
 VNLQNYVEEKLIPTWNWMVSIMDSTE AQLRYGSALASAGDPGHPNHPLHASQNSARR  
 ERMTAREEASLRTLEGRRRATLLSARQGMMSARGDFLNYALSLMRSHNDEHSDVLPV  
 LDVCSLKHVAYVFQALIYWIKAMNQQTTLDT PQLERKRTRELLELGIDNEDSEHENDDD  
 TNQSATLNDKDDDSLPAETGQNHPPFRSDSMTFLGCIPPNPFVPLAEAIPLADQPHL  
 LQPNARKEDLFGRPSQGLYSSSASSGKCLMEVTVD RNCLEVLPTKMSYAANLKNVMN  
 MQNRQKKEGEEQPVLPEETESSKPGPSAHD LAAQLKSSLLAEIGLTESEGPPLT SFRPQ  
 CSFMGMVISHDMLLGRWRLSLELFGRVFMEDVGAEPGSILTELGGFEVKESKFRREME  
 KLRNQQSRLSLEVDRDRD LLIQQTMRQLNNHFGRRCATTPMAVHRVKVTFKDEPGE  
 GSGVARSFYTAIAQAFLSNEKLPNLECIQNANKGTH TSLMQRLNRGERDRERERERE  
 MRRSSGLRAGSRRDRDRDFRRQLSIDTRPFRPASEGNPSDDPEPLPAHRQALGERLY  
 PRVQAMQPAFASKITGM LLELSPAQLLLLLASEDSL RARVDEAMELIIAHGRENGADSIL  
 DLGLVDSSEKVQQENRKRHGSSRSVVDMDLDDTDDGDDNAPLFYQPGKRGFYTPRP  
 GKNTEARLNCFRNIGRILGLCLLQNELCPITLNRHV IKVLLGRKVNWHDFAFFDPVMYES  
 LRQLILASQSSDADAVFSAMD LAFIDLCKEEGGGQVELIPNGVNIPVTPQNVYEVYRKY  
 AEHRMLVVAEQPLHAMRKGLLDVLPKNSLEDLTAEDFRLLVNGCGEVNVQMLISFTSFN  
 DESGENAEKLLQFKRWFWSIVEKMSMTERQDLVYFWTSSPSLPASEEGFQPMPSITIR  
 PPDDQHLPTANTCISRLYVPLYSSKQILKQKLLLA IKTKNFGFV

SEQ ID No:157

MATHGQTCARPMCIPPSYADLGKVARDIFNKGFGFLVKLDVKT KSCSGVEFSTSGSS  
 NTD TGKVTGTLET KYKWCEYGLTFTEKWNTDNTLGTEIAIEDQICQGLKLTFTD TTFSPNT  
 GKKS GKI KSSYKRECINLGCDVDFDFAGPAIHGSAVFGYEGWLAGYQMTFDSAKSKLT  
 RNNFAVG YRTGDFQLHTNVNDGTEFGGSIYQKVCEDLDTSVNLAWTSGTNCTRFGIAA  
 KYQLDPTASISAKVNNSSLIGVGYTQTLRPGVKLTLSALVDGKSINAGGHKVGLALELEA

SEQ ID No:158

MDSNTAPLGPSCPQPPAPQPQARSRLNATASLEQERSERPRAPGPQAGPGPGVRD  
 AAAPAEPPAQHTRSRRERADGTGPTKGDMEIPFEEVLERAKAGDPKAQTEVGKHYLQLA  
 GDTDEELNSCTAVDWLVLAQKQGRREAVKLLRRCLADRRGITSENEREVRQLSSETDL  
 ERAVRKAALVMYWKLNPKKKKQVAVAELENVGVNEHDGGAQPGVPKSLQKQRR  
 MLERLVSSSESKNYIALDDFVEITKKYAKGVIPSSLFLQDDEDDDELAKSPEDLPLRLKV  
 VKYPLHAIMEIKEYLIDMASRAGMHWLSTIIPTHHINALIFFFIISNLTIDFFAFFIPLVIFYLSF  
 ISMVICTLKVFQDSKAWENFRTLTDLLRFEPNLDVEQAEVNFNGWNHLEPYAHFLLSVFF  
 VIFSFPISKDCIPCSELAVITGFFTVTSYLSLSTHAEPYTRRALATEVTAGLLSLLPSMPL  
 NWPYLVKVLGQTFITVPVGHVVLNVSVPCLLYVYLLYLFFRMAQLRNFKGTICYLVPYLV  
 CFMWCELSVVILLESTGLGLLRASIGYFLFLFALPILVAGLALVGVLQFARWFTSLELT  
 KIA VTVAVCSVPLLLRWWTKASFVVGMMVKSLTRSSMVKLILVWLTAIVLFCWFYVYRSEGM  
 KVINSTLTWQQYGALCGPRAWKETNMARTQILCSHLEGHRVTWTGRFKYVRVTDIDN  
 SAESAINMLPFFIGDWMRCLYGEAYPACSPGNTSTAEELCRLKLLAKHPCHIKKFD  
 RY KFEITVGMPSGADGSRSDREDDVT KDIVLRASSEFKSVLLSLRQGS  
 LIEFSTILEGRLG SKWPVFELKAISCLNCMAQLSPTRRHVKIEHDWRSTVHGAVKFAFD  
 FFFFPFLSAA

SEQ ID No:159

MAAAVQGGRRSGGSGGCSGAGGASNCGTGSGRSGLLDKWKIDDKPKIDKWDGSAV  
 KNSLDDSAKKVLEKYKYVENFGLIDGRLTICTISCFFAIVALIWDYMHFPFESKPV  
 LALC VISYFVMMGILTIYTSYKEKSIFLVAHRKDPTGMDPDIDWQLSSSLKRFDDKY  
 TLKLTIFIS GR TKQQREAEFTKSIKFFDHSGTLVMDAYEPEISR LHDSLAIERKIK

SEQ ID No:160

MAVLRQLALLLWKNYTLQKRKVLTVLELFLPLLFPGLIWLRLKIQSENVPNATIYPGQSI  
 QELPLFFTFPPPGDTWELAYIPSHSDAAKTVTETVRRALVINMRVRGFPSEKDFEDYIRY  
 DNCSSSVLAADVFEHPFNHSKEPLPLAVKYHLRFSYTRRNYMWTQTGSFFLKETEGWH  
 TTSFLPLFPNPGPRELTSPDGGEPGYIREGFLAVQHAVDRAIMEYHADAATRQLFQRLT  
 VTIKRFPPYPPFIADPFLVAIQYQLPLLLLLSFTYTALTARAVVQEKERRLKEYMRMMGLS  
 SWLHWSAWFLLFFLFLIAASFMTLLFCVKVKNVAVLSRSDPSLVLAFLLCFAISTISFSF  
 MVSTFFSKANMAAAF GGFLYFFTYIPYFFVAPRYNWM TSLSQKLCSCLLSNVAMAMGAQ  
 LIGKFEAKGMGIQWRDLLSPVNVDDDFCFGQVLGMLLLDSVLYGLVTWYMEAVFPGQF  
 GVPQPWYFFIMPSYWCGKPRAVAGKEEEDSDPEKALRNEYFEAEPEDLVAGIKIKHLSK

VFRVGNKDRAAVRDLNLNLYEGQITVLLGHNGAGKTTTLSMLTGLFPPTSGRAYISGYEI  
SQDMVQIRKSLGLCPQHDLFDNLTVAEHLYFYAQLKGLSRQKCPEEVKQMLHIIGLEDK  
WNSRSRFLSGGMRRKLSIGIALIAGSKVLILDEPTSGMDAISRRAIWDLLQRQKSDRTIVL  
TTHFMDEADLLGDRIAIMAKGELQCCGSSLFLKQKYGAGYHMTLVKEPHCNPEDISQLV  
HHHVPNATLESSAGAELSFILPRESTHRFEGLFAKLEKKQKELGASFGASITTMEEVFLR  
VGKLVDSMDIQAIQLPALQYQHERRASDWAVDSNLCGAMDPSDGIGALIEEERTAVKL  
NTGLALHCQQFWAMFLKKAAYSWREWKMVAAQVLVPLTCVTLALLAINYSSSELFDDPM  
LRLTLGEYGRTVVPFSVPGTSQLGQQQLSEHLKDALQAEGQEPREVLGDLEEFLIFRASV  
EGGGFNERCLVAASFRDVGERTVVNALFNNQAYHSPATALAVVDNLLFKLLCGPHASIV  
VSNFPQPRSAALQAAKDQFNEGRKGFDIALLNFAMAFLASTFSILAVSERAVQAKHVQF  
VSGVHVASFWSALLWDLISFLIPSLLLLWVFAFDVRAFTRDGHMADTLLLLLLYGWAI  
PLMYLMNFFFLGAATAYTRLTIFNILSGIATFLMVTIMRIPAVKLEELSKTLDHVFLVLPNH  
CLGMAVSSFYENYETRRYCTSSSEVAHYCKKYNIQYQENFYAWSAPGVGRFVASMAA  
SGCAYLILLFLIETNLLQRLRGILCALRRRRTLTELYTRMPVLPEDQDVADERTRILAPSP  
DSLLHTPLIIKELSKVYEQRVPLLAVDRLSLAVQKGECFLLGFNGAGKTTTTFKMLTGEE  
SLTSGDAFVGGHRISSDVGKVRQRIGYCPQFDALLDHMTGREMLVMYARLRGIPERHI  
GACVENTLRGLLLEPHANKLVRTYSGGNKRKLSTGIALIGEPVIFLDEPSTGMDPVARR  
LLWDTVARARES GKAIITSHSMEECEALCTRLAIMVQGQFKCLGSPQHLKSKFGSGYSL  
RAKVQSEGQQEAL EEFKAFVDLTFPGSVLEDEHQGMVHYHLPGRDLSWAKVFGILEKA  
KEYGVDDYSVSQISLEQVFLSFAHLQPPTAE EGR

SEQ ID No:161

MAQALPWLLLWMGAGVLP AHGTQH GIRLPLRSGLG GAPLGLRLPRETDEEPEEPGRR  
GSFVEMVDNLRGKSGQGYYVEMTVGSPQTNLILVDTGSSNFAVGAAPHPFLHRY YQ  
RQLSSTYRDLRKG VYPYTQ GKWEGELGTDLV SIPHGPNVTVRANIAAITESDKFFINGS  
NWE GILGLAYAEIARPDDSL EPPFD SLVKQTHVPNLFS LQLCGAGFPLNQSEVLASVGG  
SMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN  
LRLPKKVFEAAVKS IKAASSTEKFPD GFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVT  
NQSF RITLPQQYL RPPVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRI  
GFAVSACHVHDEFRTAAVEGPFVTLDMEDCGYNIPQTDESTLMTIAYVMAAICALFMLP  
LCLMVCQWRCLRCLRQQHDDFADDISLLK

SEQ ID No:162

MSEADGLRQRRPLRPQVVTDDDGQAPEAKDGSSFSGRVFRVTFLMLAVSLTVPLLGA  
MMLLESPIDPQPLSFKEPPLLLGVLHPNTKLRQAERLFENQLVGPESIAHIGDVMFTGTA  
DGRVVKLENGEIETIARFGSGPCKTRDDEPVCGRPLGIRAGPNGTLFVADAYKGLFEVN  
PWKREVKLLLSSETPIEGKNMSFVNDLTVTQDGRKIYFTDSSSKWQRRDYLLLVMEGT  
DDGRLLEYDTVTREVKVLLDQLRFPNGVQLSPAEDFVLVAETTMARIRRVYVSGLMKG  
GADLFVENMPGFPDNIRPSSSGGYWVGMSTIRPNPGFSMLDFLSERPWIKRMIFKLFS  
QETVMKFVPRYSLVLELSDSGAFRRSLHDPDGLVATYISEVHEHDGHLYLGSFRSPFLC  
RLSLQAV

SEQ ID No:163

MSFLIDSSIMITSQILFFGFGWLFFMRQLFKDYEIRQYVQVIFSVTFAFSCTMFELIIFEIL  
GVLNSSSRYPFWKMNLCVILLILVMVPFYIGYFIVSNIRLLHKQRLLFSCLLWLTFMYFF  
WKLGDPPFIPSPKHGILSIEQLISRVGVIGVTLMALLSGFGAVNCPYTYMSYFLRNVTDTD  
ILALERRLLQTMDMIISKKKRMAMARRTMFQKGEVHNKPSGFWGMIKSVTTSASGSEN  
TLIQQEVDAL EELSRQLFLETADLYATKERIEYSKTFKGKYFNFLGYFFSIYCVWKIFMATI  
NIVFDRVGKTDPVTRGIEITVNYLGIQFDVKFWSQHISFILVGIIIVTSIRGLLITLTKFFYAI  
SSKSSNVIVLLLAQIMGMYFVSSVLLIRMSMPLEYRTIITEVLGELQNFYHRWFDVIFLVS  
ALSSILFLYLAHKQAPEKQMAP

SEQ ID No:164

MSSSEEVSWISWFCGLRGNEFFCEVDEDYIQDKFNLTGLNEQVPHYRQALDMILDLEP  
DEELEDNPNQSDLIEQAAEMLYGLIHARYILTNRGIAQMLEKYQQGDFGYCPRVYCENQ  
PMLPIGLSDIPGEAMVKLYCPKCMDVYTPKSSRHHHTDGAYFGTGFPHMLFMVHPEYR  
PKRPANQFVPRLYGFKIHPMAYQLQLQAASNFKSPVKTIR

SEQ ID No:165

MWQLWASLCCLLVLANARSRPSFHPVSDELVNYVNKRNTTWQAGHNFYNVDMSYLKR  
LCGTFLGGPKPPQRMFTEDLKLPASFDAREQWPQCPTIKEIRDQGSCGSCWAFGAV  
EASDRICIHNTNAHVSVEVSAEDLLTCCGSMCGDGCNGGYPAEAWNFWTRKGLVSGGL  
YESHVGCRPYSIPPCEHHVNGSRPPCTGEGDTPKCSKICEPGYSPTYKQDKHYGYNSY  
SVSNSEKDIMAIEYKNGPVEGAFSVYSDFLLYKSGVYQHVTGEMMGGHAIIRILGWGVE  
NGTPYWLANSWNTDWGDNGFFKILRGQDHCGIESEVVAGIPRTDQYWEKI

SEQ ID No:166

MGKGGNQGEAAEREVSPTFSWEEIQKHNLRTDRWLVIDRKVYNITKWSIQHPGGQ  
 RVIGHYAGEDATDAFRAFHPDLEFVGKFLKPLLIGELAPEEPSQDHGKNSKITEDFRALR  
 KTAEDMNLFKTNHVFFLLLLAHIIALESIAWFTVIFYFGNGWIPTLITAFVLATSQAQAGWL  
 QHDYGHLSVYRKPKWNHLVHKFVIGHLKGASANWWNHRHFQHHAKPNIFHKDPDVNM  
 LHVFLGEWQPIEYGKKKLKYL PYNHQHEYFFLIGPPLLIPMYFQYQIIMTMIVHKNWVDL  
 AWAVSYYIRFFITYIPFYGILGALLFLNFIRFLESHWFVWVTQMNHIVMEIDQEAYRDWFS  
 SOLTATCNVEQSFFNDWFSGHLNFQIEHHLFPTMPRHNHAKIAPLVKSLCAKHGIEYQE  
 KPLL RALLDIIRSLKKSGKLWLDAYLHK

SEQ ID No:167

MASLDRVKVLVLGD SGVGKSSLVHLLCQNQVLGNPSWTVGCSVDVRVHDYKEGTPEE  
 KTCYIELWDVGGSGVSASSVKSTRAVFYNSVNGIIFVHDLTNKKSSQNLRRWSLEALNR  
 DLVPTGVLVTNGDYDQEQFADNQIPLLIGTKLDQIHETKRHEVLTTTAFLAEDFNPEEIN  
 LDCTNPRYLAAGSSNAVKLSRFFDKVIEKRYFLREGNQIPGFPDRKRFGAGTLKSLHYD

SEQ ID No:168

MRRLTRRLVLPVFGVLWITVLLFFWVTKRKLEVPTGPEVQTPKPSDADWDDLWDQFDE  
 RRYLNAKKWRVGGDPYKLYAFNQRESERISSNRAIPDTRHLSVLNRTPTHLIREIILVDDF  
 SNDDPDDCKQLIKLPVKCLRNNERQGLVRSRIRGADIAQGTTLTFLDSHCEVN RDWLQP  
 LLHRVKEDYTRVVCVIDIINLDTFTYIESASELRGGFDWLSLHFQWEQLSPEQKARRLDP  
 TEPIRTPIIAGGLFVIDKAWFDYLGKYDMDMDIWGGENFEISFRVWMCSSSLEIVPCSRV  
 GHVFRKKHPYVFPDGNANTYIKNTKRTAEVWMDEYKRYYYAARPFALERPFGNVESRL  
 DLRKNLRCQSFKWYLENIYPELSIPKESSIQKGNIRQRQKCLESQANGTTGSSGQRPAG  
 GTSEIWVQKPRVRNRRHAAPQGFDPGAKPSQHWRRPEHPAAE

SEQ ID No:169

MFFSMGFIVAVKGKIASPLEAPVFVAAPHSTFFDGIACVVAGLPSMVSRNENAQVPLIGR  
 LLRAVQPVLVSRVDPDSRKNTINEIIRTTSGGEWQPILVFPEGTCTNRSLITFKPGAFI  
 PGVPVQPVLLRYPNKLDTVTWTWQGYTFIQLCMLTFCQLFTKVEVEFMPVQVPNDEEK  
 NDPVLFANKVRNLMAEALGIPVTDHTYEDCRLMISAGQLTLPMEAGLVEFTKISRKLKLD  
 WDGVRKHLDEYASIASSSKGGRIIEFAKYLKLPVSDVLRQLFALFDRNHDGSIDFREY  
 VIGLAVLCNPSNTEEIIQVAFKLFVDVDEDDGYITEEEFSTILQASLGVPDL DVSGLFKEIAQG  
 DSISYEEFKSFALKHPEYAKIFTTYLDLQTCHVFSLPKEVQTTPSTASNKVSPEKHEEST  
 SDKKDD

SEQ ID No:170

MRPRRPHQIADLFRPKDQIAYSDTSPFLILSEASLADLNSRLEKKVKATNFRPNIVISGCD  
VYAEDSWDELLIGDVELKRVMACSRCILTTVDPTGVMSRKEPLETLKSYRQC DP SERK  
LYGKSPLFGQYFVLENPGTIKVGDPVYLLGQ

SEQ ID No:171

MAATALLEAGLARVLFYPTLLYTLFRGKVPGRAHRDWYHRIDPTVLLGALPLRSLTRQLV  
QDENVRGVITMNEEYETRFLCNSSQEWKRLGVEQLRLSTVDMTGIPTLDNLQKGVQFA  
LKYQSLGQC VYVHCKAGR SRSATMVAAYLIQVHKWSPEEAVRAIAKIRSYIHIRPGQLDV  
LKEFHKQITARATKDGT FVISKT

SEQ ID No:172

MSSF GYRTL TVALFT LICCPGSDEKVF EVHVRPKKLAVEPKGSLEVNCSTTCNQPEVGG  
LETSLNKILLDEQAQWKHYLVSNISHDTV LQCHFTCSGKQESMNSNVSVYQPPRQVILT  
LQPTLVAVGKSFTIECRVPTVEPLDSLTLFLFRGNETLHYETFGKAAPAPQEATATFNST  
ADREDGHRNFSCLA VLDLMSRGGNIFHKHSAPKMLEIYEPVSDSQMVII VTVSVLLSLF  
VTSVLLCFIFGQH LRQQRMGTYGVRAAWRRLPQA FRP

SEQ ID No:173

ASGEWRVSGGRPAGAGRPEEALAAGSDPRGAAARLACSAPT PGGGTMPFD FRRFDIY  
RKVPKDLTQPTYTGAIISICCLFILFLFLSELTGFITTEVVNELYVDDPDKDSGGKIDVSL  
NISLPNLHCELVGLDIQDEMGRHEVGHIDNSMKIPLNNGAGCRFEGQFSINKVPGNFHV  
STHSATAQPQNPD MTHVIHKLSFGDTLQVQNIHGAFNALGGADRLTSNPLASHDYILKIV  
PTVYEDKSGKQRYSYQYTVANKEYVAYSHTGRIIPAIWFRYDLSPITVKYTERRQPLYRF  
ITTICAIIGGTFTVAGILDSCIFTASEAWKKIQLGKMH

SEQ ID No:174

NSKKMQSWYSMLSPTYKQRNEDFRKLFSKLPEAERLIVDYSCALQREILLQGRLYLSEN  
WICFYSNIFRWETTISIQLKEVTCLKKEKTAKLIPNAIQICTESEKHFFTSFGARDRCFLIF  
RLWQNALLEKTLSPRELWHLVHQCYGSELGLTSEDEDYVSP LQLNGLGTPKEVGDVIA  
LSDITSSGAADRSQEPSVGSRRGHVTPNLSRASSDADHGAEEDKEEQVDSQPDASS  
SQT VTPVAEPPSTEPTQPDGPTTLGPLDLLPSEELLTDTSNSSSSTGEEADLAALLPDLS  
GRLLINSVFHVGAERLQQMLFSDSPFLQGFLQQCKFTDVTLSPWSGDSKCHQRRVLT Y

TIPISNPLGPKSASVVETQTLFRRGPQAGGCVVDSEVLTQGIPYQDYFYTAHRYCILGLA  
 RNKARLRVSSEIRYRKQPWSLVKSLIEKNSWSGIEDYFHHLERELAKAEKLSLEEGGKD  
 ARGLLSGLRRRRKRPLSWRAHGDGPQHDPDPDCARAGIHTSGSLSSRFSEPSVDQGGPG  
 AGIPSALVLISIVSLIILIALNVLLFYRLWSLERTAHTFESWHSALAKGKFPQTATEWAEIL  
 ALQKQFHSVEVHKWRQILRASVELLDEMKFSLEKLHQGITVSDPPFDTQPRPDDSF

SEQ ID No:175

MLGLLVALLALGLAVFALLDVWYLVRLPCAVLRARLLQPRVRDLLAEQRFPGRVLPDDL  
 DLLLHMNNARYLREADFARVAHLTRCGVLGALRELRAHTVLAASCARHRRSLRLLPEFE  
 VRTRLLGWDDRAFYLEARFVSLRDGFVCALLRFRQHLLGTSPERVVQHLQRRVEPPE  
 LPADLQHWISYNEASSQLLRMESGLSDVTKDQ

SEQ ID No:176

MTLARFVLALMLGALPEVVGFDVNLDSLHSHSRHSPPAGPHYPPYLPTQQRPPTRP  
 PPPLPRFPRPPRALPAQRPHALQAGHTPRPHPWGCPAGEPWVSVTDFGAPCLRWAE  
 VPPFLERSPPASWAQLRGQRHNFCSRSPDGAGRPWCFYGDARGKVDWGYCDCRHGS  
 VRLRGGKNEFEGTVEVYASGVWGTVCSSHWDDSDASVICHQLQLGGKGIKQTPFSG  
 LGLIPIYWSNVRCRGDEENILLCEKDIWQGGVCPQKMAAAVTCSFSHGPTFPIIRLAGGS  
 SVHEGRVELYHAGQWGTVCDDQWDDADADEVICRQLGLSGIAKAHQAYFGEGSGPV  
 MLDEVRCCTGNELSIEQCPKSSWGEHNCGHKEDAGVSCTPLTDGVIRLAGGKGSHEGR  
 LEVYYRGQWGTVCDDGWTELNTYVVCRLGFKYKGKQASANHFEESTGPIWLDDVSCS  
 GKETRFLQCSRRQWGRHDCSHREDVSIACYPGGEGHRLSLGFPVRLMDGENKKEGR  
 VEVFINGQWGTICDDGWTDKDAVICRQLGYKGPARARTMAYFGEGKGPIHVDNVKCT  
 GNERSLADCIKQDIGRHNCRHSEDAGVICDYFGKKASGNSNKESSLSSVCGLRLLHRRQ  
 KRIIGGKNSLRGGWPWQVSLRLKSSHGDGRLLCGATLLSSCWVLTAAHCFKRYGNSTR  
 SYAVRVGDYHTLVPEEFEEEEIGVQQIVIHREYRPDRSDYDIALVRLQGPEEQCARFSSH  
 VLPACLPLWRERPQKTASNCYITGWGDTGRAYSRTLQQAAPLLPKRFCEERYKGRFT  
 GRMLCAGNLHEHKRVDSCQGDSGGPLMCERPGEWVYGVTSWGYGCGVKDSPGV  
 YTKVSAFVPWIKSVTKL

SEQ ID No:177

MEPGTGGSRKRLGPRAGFRFWPPFFPRRSQAGSSKFPTPLGPENSGNPTLLSSAQPE  
 TRVSYWTKLLSLLAPLPGLLQKVLWSQLFGGMFPTRWLDFAGVYSALRALKGREKP  
 AAPTAKSLSSLQLDSSDPSVTSPLDWLEEGIHWQYSPPDLKLELKAKGSALDPAAQAF

LLEQQLWGVELLPSSLQSRLYSNRELGSSPSGPLNIQRIDDFSUVSYLLNPSYLD CFPRL  
 EVSYQNSDGNSEVVGFQTLTPESSCLREDHCHPQPLSAELIPASWQGCPLSTEGLPEI  
 HHLRMKRLEFLQQASKGQDLPTPDQDNGYHSLEEEHSLLRMDPKHCRDNPTQFVPAA  
 GDIPGNTQESTEEKIELLTTEVPLALEEESPSEGCPSSSEIPMEKEPGEGRISVVDYSYLE  
 GDLPISARPACSNKLIDYILGGASSDLETSSDPEGEDWDEEAEDDGFSDSDSSLSDSDLE  
 QDPEGLHLWNSFCSDVPYNPQNFTATIQTAA RIVPEEPSDSEKDLSGKSDLENSSQSG  
 SLPETPEHSSGEEDDWESSADEAESLKLWNSFCNSDDPYNPLNFKAPFQTSGENEKG  
 CRDSKTPSESIVASECHTLLSCKVQLLGSQESECPDSVQRDVLSGGRHTHVKRKKVTF  
 LEEVTEYYISGDEDRKGPWEEFARDGCRFQKRIQETEDAIGYCLTFEHRERMFNRLQG  
 TCFKGLNVLKQC

SEQ ID No:178

MAAETLLSSLLGLLLLGLLL PASLTGGVGSLNLEELSEMRYGIEILPLPVMGGQSQSSDV  
 VIVSSKYKQRYECRLPAGAIHFQREREEETPAYQGPGIPELLSPMRDAPCLLKT KDWWT  
 YEFYGRHIQQYHMEDSEIKGEVLYLGYYSQSAFDWDDetakaskQHRLKRYHSQTYG  
 NGSKCDLNGRPREA EVRFLCDEGAGISGDYIDRVDEPLSCSYVLTIRT PRLCPHPLLRP  
 PPSAAPQAILCHPSLQPEEY MAYVQRQADSKQYGDKII EELQDLGPQVWSETKSGVAP  
 QKMAGASPTKDDSKDSDFWKMLNEPEDQAPGGEEVPAEEQDPSPEAADSASGAPND  
 FQNNVQVKVIRSPADLIRFIEELKGGTKKGKPNIGQE QPVDDAAEVPQREPEKERGDPE  
 RQREMEEEEEDEDEDEDEDEDERQLLGEFEKELEGILLPSDRDRLRSEVKAGMERELN  
 IIQETEKELDPDGLKKESERDRAMLALTSTLNKLIK RLEEKQSPELVKKHKKKRVVPKKP  
 PPSPQPTEEDPEHRVRVRVTKLRLGGPNQDLTVLEMKREN PQLKQIEGLVKELLEREG  
 LTAAGKIEIKIVRPWAEGTEEGARWLTDEDTRNLKEIFFN ILVPGAEAAQKERQRQKELE  
 SNYRRVWGSPGGEGTGDLDEFDF

SEQ ID No:179

MAVVPLLLLGG LWSAVGASSLG VVTCGSVVKLLNTRHNVRLHSHD VRYGSGSGQQSV  
 TGVTSVDDSNSYWRIRGKSATVCERGTPiKCGQPIRLTHVNTGRNLHSHHFTSPLSGN  
 QEVSAFGEEGEGDYLD DWTVLCNGPYWVRDGEVRFKHSSTEVL LSVTGEQYGRPI SG  
 QKEVHGMAQPSQNNYWKAMEGIFMKPSELLKAEAHHAEL

SEQ ID No:180

MEASGKLICRQRQVLF SFLLLGLSLAGAAEPRSYSV EETEGSSFVTNLAKDLGLEQRE  
 FSRRGVRVVS RGNKLHLQLNQETADLLLNEKLDREDLCGHTEPCVLR FQVLLES PFEFF

QAEQVIDINDHSPVFLDKQMLVKVSESSPPGTAFPLKNAEDLDIGQNNIENYIISPNSYF  
 RVLTRKRS DGRKYPELVLDNALDREEEAELRLTLTALDGGSPPRSGTAQVYIEVVDVND  
 NAPEFQQPFYRVQISEDSPISFLVVKVSATDVD TG VNGEISYSLFQASDEISKTFKVDFLT  
 GEIRLKKQLDFEFQSYEVNIEARDAGGFSGKCTVLIQVIDVNDHAPEVTMSAFTSPIPE  
 NAPETVVALFSVSDLDSENGKISCSIQEDLPFLLKSSVGNFYTLTTETPLDRESRAEYN  
 VTITVTDLGT PRLTTHLNMTVLVSDVNDNAPAFTQTSYTLFVRENNSPALHIGSVSATDR  
 DSGTNAQVTYSLLPPQDPHPLASLVSINTDNHGLFALRSLDYEALQAFEFVVGASDRG  
 SPALSSEALVRVLVDANDNSPFVLYPLQNGSAPCTELVPRAAEPGYLVTKVVAVDGDS  
 GQNAWLSYQLLKATEPGLFGVWAHNGEVRTARLLSERDAAKQRLVVLVKDNGEPPCS  
 ATATLHLLLV DGF SQPYLPLPEAAPAQGGADSLTVYLVALASVSSLFLFSVLLFVAVLLC  
 RRSRAASVGRCSVPEGPFP GHLVDVRGTGSL SQNYQYEVCLAGGSGTNEFQFLKPVL  
 PNIQGHSGPEMEQNSNFRNGFGFSLQLK

SEQ ID No:181

MASRGVVGIFFLSAVPLVCLELRRGIPDIGIKDFLLCGRILLLLALLTLISVTTSWLNSFKS  
 PQVYLKEEEEKNEKRQKLVRKKQQEAQGEKASRYIENVLKPHEMKLRKLEERFYQMT  
 GEAWKLSSGHKLGGDEGTSQTSFETSNREAAKSQNLPKPLTEFPSPA EQPTCKEIPDL  
 PEEPSQTAEVVTV ALRCPSGNVLRRRFLKSYSSQVLF DWMTRIGYHISLYSLSTSFP  
 RPLAVEGGQSLEDIGITVDTVLILEEKEQTN

SEQ ID No:182

MAAAEEEDGGPEGPNRERGGAGATFECNICLETAREAVVSVC GHLYCWPC LHQWLET  
 RPERQECVPCKAGISREKVPLYGRGSQKPQDPRLKTPPRPQGQRPAPE SRGGFQPF  
 GDTGGFHFSFGVGAFPPFGFFTTVFNAHEPFRRGTGVDLGQGH PASSWQDSLFLFLAIF  
 FFFWLLSI

SEQ ID No:183

MKFLLDILLLLPLLIVCSLESFVKLFIPKRRKSVTGEIVLITGAGHGIGRLTAYEFAKLKSKL  
 VLWDINKHGLEETAACKGLGAKVHTFVWDCSNREDIYSSAKKVKA EIGDVSILVNNAGV  
 VYTSDLFATQDPQIEKTFEVNVLAHFWTTKAFLPAMTKNNHGHIVTVASAAGHVSVPFLL  
 AYCSSLKFAAVGFHKTLTDELAALQITGVKTTCLCPNFVNTGFIKNPSTSLGPTLEPEEV  
 NRLMHGILTEQKMIFIPSSIAFLTTLERILPERFLAVLKRKISVKF DAVIGYKMKQAQ

SEQ ID No:184

MWSAGRGGAAWPVLLGLLLALLVPGGGAAGTGAELVTCGSVLKLLNTHHRVRLHSHDI  
 KYGSGSGQQSVTGVEASDDANSYWRIRGGSEGGCPCGSPVRCGQAVRLTHVLTGKN  
 LHTHHFPSPLSNNQEVSFAFGEDGEEDDLWTVRCSGQHWEREAAVRLQHVGTSVFL  
 SVTGEQYGSPIRGQHEVHGMP SANTHNTWKAMEGIFIKPSVEPSAGHDEL

SEQ ID No:185

GRWASGEMAPSGSLAVPLAVLVLLLWGAPWTHGRRSNVRVITDENWRELLEGDWMIE  
 FYAPWCPACQNLQPEWESFAEWGEDLEVNIKVDVTEQPGLSGRFIITALPTIYHCKDG  
 EFRRYQGPRTKKDFINFISDKEWKSIEPVSSWFPGPSVLMSSMSALFQLSMWIRTCHN  
 YFIEDLGLPVWGSYTVFALATLFSGLLLGLCMIFVADCLCPSKRRRPQYPYPYPSKLLSE  
 SAQPLKKVEEEQEAEDEEDVSEEEAESKEGTNKDFPQNAIRQRSLGPSLATDKS

SEQ ID No:186

AVPPTYADLGKSARDVFTKGYGFGLIKLDLKTSENGLEFTSSGSANTETTKVTGSLETK  
 YRWTEYGLTFTEKWNTDNTLGTEITVEDQLARGLKLTFDSSFSPTNGKKNKIKTGKYN  
 EHINLGCDMDFDIAGPSIRGALVLGYEGWLAGYQMNFETAKSRVTQSNFAVGKTDDEF  
 QLHTNVNDGTEFGGSIYQKVNKKLETAVNLAWTAGNSNTRFGIAAKYQIDPDACFSAKV  
 NNSSLIGLGYTQTLKPGIKLTLSALLDGKNVNAGGHKLGLGLEFQA

SEQ ID No:187

MAKNRRDRNSWGGFSEKTYEWSSEEEEPVKKAGPVQVLIVKDDHSFELDETALNRILL  
 SEAVRDKEVVAVSVAGAFRKGKSFLMDFMLRYMYNQESVDWVG DYNEPLTGFSWRG  
 GSERETTGIQIWSEIFLINKPDGKKVAVLLMDTQGTQSTLRDSATVFALSTMISSIQV  
 YNLSQNVQEDDLQHLQLFTEYGR LAMEETFLKPFQSLIFLVRDWSFPYEF SYGADGGA  
 KFLEKRLKVSGNQHEELQNVKRKHIHSCFTNISCFLPHPLGLKVATNP NFDGKLKEIDDEFI  
 KNLKILIPWLLSPESLDIKEINGNKITCRGLVEYFKAYIKIYQGEELPHPKSMLQATAEANN  
 LAAVATAKDTYNKKMEEICGGDKPFLAPNDLQTKHLQLKEESVKLFRGVKKMGGEFFS  
 RRYLQQLESEIDELIYIYIKHNDSKNIFHAARTPATLFFVIFITYVIAGVTGFIGLDIIASLCN  
 MIMGLTLITLCTWAYIRYSGEYRELGAVIDQVAAALWDQGSTNEALYKLYSAAATHRHLY  
 HQAFPTPKSESTEQSEKKKM

SEQ ID No:188

VGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRM TTTSSVEGKQNLVIMGKKTWF  
 SIPEKNRPLKGRINLVLSRELKEPPQGAHFLSRSLDDALKLTEQPELANKVDMVWIVGG

SSVYKEAMNHPGHLKLFVTRIMQDFESDTFFPEIDLEKYKLLPEYPGVLSDVQEEKGIKY  
KFEVYEKND

SEQ ID No:189

MGPGRPAPAPWPRHLLRCVLLLGCLHLGRPGAPGDAALPEPNVFLIFSHGLQGCGLEAQ  
GGQVRVTPACNTSLPAQRWKWVSRNRLFNLTGMQCLGTGWPGTNTTASLGMYECDR  
EALNLRWHCRTLGDQLSLLGARTSNISKPGTLERGDQTRSGQWRIYGSEEDLCALPY  
HEVYTIQGNSHGKPCTIPFKYDNQWFHGCTSTGREDGHLWCATTQDYGKDERWGFC  
PIKSND CETFWDKDQLTDSCYQFNFQSTLSWREAWASCEQQGADLLSITEIHEQTYING  
LLTGYSSTLWIGLNDLDTSGGWQWSDNSPLKYLNWESDQPDNPSEENCGVIRTESSG  
GWQNRDCSIALPYVCKKKPNATAEPTPPDRWANVKVECEPSWQPFQGH CYRLQAEK  
RSWQESKKACLRGGGDLVSIHSM AELEFITKQIKQEVEELWIGLNDLKLQMNFEWSDG  
SLVSFTHWHPFEPNNFRDSLED CVTIWGPEGRWNDSPCNQSLPSICKKAGQLSQGAA  
EEDHGCRKGWTWHSPSCYWLGEDQVTYSEARRLCTDHGSQLVTITNRF EQAFVSSLI  
YNWEGEYFWTALQDLNSTGSFFWLSGDEV MYTHWNRDQPGYSRGGCVALATGSAM  
GLWEVKNCTSF RARYICRQSLGTPVTPELPGPDPTPSLTGSCPQGWASDTKLRYCYKV  
FSSERLQDKKSWVQAQGACQELGAQLLSLASYEEEHFVANMLNKIFGESEPEIHEQHW  
FWIGLNRDRPRGGQSWRWS DGVGFSYHNFD RSRHDDDDIRGCAVL DLASLQWVAMQ  
CDTQLDWICKIPRGTDVREPDDSPQGRREWLR FQEAEYKFFEHHSTWAQAQRCTWF  
QAELTSVHSQAELD FLSHNLQKFSRAQE QHWWIGLHTSESDGRFRWTDGSIINFISWA  
PGKPRPVGKDKKCVYMTASREDWGDQRCLTALPYICKRSNVTKETQPPDLPTTALGG  
CPSDWIQFLNKCFVQVQGQEPQSRVKWSEAQFSCEQQEAQLVTITNPLEQAFITASLPN  
VTFDLWIGLHASQRDFQWVEQEPLMYANWAPGEPSPGSPAPSGNKPTSCAVVLHSPS  
AHFTGRWDDRSCTEETHGFICQKGTDP SLSPSPAALPPAPGT ELSYLN GTFRLLQKPLR  
WHDALLLCESHNASLAYVPDPYTQAFLTQAARGLRTP LWIGLAGEEGSR RYSWVSEEP  
LNYVGWQDGEPQQPGGCTYVDVDGAWRTTSCDTKLQGAVCGVSSGPPPPRRISYHG  
SCPQGLADSAWIPFREHCYSFHMELL LGHKEARQRCQRAGGAVLSILDEMENVFVWE  
HLQSYEGQSRGAWLG MNFNPKGGTLVWQDNTAVNYSNWGPPGLGPSMLSHNSCYW  
IQSNSGLWRPGACTNITMGVVCKLPRAEQSSFSPSALPENPAALVVVLM AVL LLLALLTA  
ALILYRRRQSIERGAFEGARYSRSSSSPTEATEKNILVSDMEMNEQQE

SEQ ID No:190

MEDHQHVPIDIQTSKLLDWLVDRRHCSLKWQSLVLTIREKINAAIQDMP ESEEIAQLLSG  
SYIHYFHCLRILDLLKGTEASTKNIFGRYSSQRMKDWQEIIALYEKDNTYLVELSSLLVRN

VNYEIPSLKKQIAKCQQLQQEYSRKEEECCQAGAAEMREQFYHSCKQYGITGENVRGEL  
 LALVKDLPSQLAEIGAAAQQSLGEAIDVYQASVGFVCESPTEQVLPMLRFVQKRGNSTV  
 YEWRTGTEPSVVERPHLEELPEQVAEDAIDWGDFGVEAVSEGTDSGISAEAAAGIDWGI  
 FPESDSKDPGGDGIDWGDDAVALQITVLEAGTQAPEGVARGPDALTLEYTETRQFL  
 DELMELEIFLAQRAVELSEEADVLSVSQFQLAPAILQGQTKEKMVTMVSVLEDLIGKLT  
 LQLQHLMILASPRYVDRVTEFLQQKCLKQSLLALKKELMVQKQQAEEQAALPKLD  
 LLEKTKELQKLIADISKRYSGRPVNLMTSL

SEQ ID No:191

GGRQRCQRGRSCGAREEEVEPGTARPPPAASAMDASLEKIADPTLAEMGKNLKEAVK  
 MLEDSSQRTEEENGKKLISGDIPGLQGSGQDMVSILQLVQNLMHGDEDEEPQSPRIQ  
 NIGEQQHMLLGHSLGAYISTLDKEKLRKLTTRILSDTTLWLCRIFRYENGCAIFYHEER  
 EGLAKICRLAIHSRYEDFVVDGFFVLYNKKPVIYLSAAARPGLGQYLCNQLGLPFPCLCR  
 VPCNTVFGSQHQMDVAFLEKLIKDDIERGRLPLLLVANAGTAAVGHTDKIGRLKELCEQ  
 YGIWLHVEGVNLTALALGYVSSSVLAAAKCDSMTMTPGPWLGLPAVPAVTLYKHDDPA  
 LTLVAGLTSNKPTDKLRALPLWLSLQYLGLDGFVERIKHACQLSQRLQESLKKVNYIKILV  
 EDELSSPVVFRFFQELPGSDPVFKAVPVNMTPSGVGRERHSCDALNRWLGEQLKQ  
 LVPASGLTVMLEAEGTCLRFSPMLTAAVLGTRGEDVDQLVACIESKLPVLCCTLQLRE  
 EFKQEVEATAGLLYVDDPNWSGIGVVRYEHANDDKSSLKSDPEGENIHAGLLKKLNELE  
 SDLTFKIGPEYKSMKSCLYVGMASDNVDAAELVETIAATAREIEENSRLLENMTEVVRKG  
 IQEAQVELQKASEERLLEEGVLRQIPVVGSVLWVSPVQALQKGRTFNLTAGSLESTEPI  
 YVYKAQGAGVTLPTPSGSRTKQRLPGQKPFKRSLRGSDALSETSSVSHIEDLEKVERL  
 SSGPEQITLEASSTEGHPGAPSPQHTDQTEAFQKGVPHPEDDHSQVEGPESLR

SEQ ID No:192

EPCALTPGPSHLALTFLPSKPGARPQPEGASWDAGPGGAPSAWADPGEGGPSPMLLP  
 EGLSSQALSTEAPLPATLEPRIVMGEETCQALLSPRAARTALRDQEGGHASPDPPPELC  
 SQGDL~~SVPSPPDPDSFFTP~~STPTKTTYALLPACGPHGDARDSEAELRDELDSPPAS  
 PSGSYITADGDSWASSPSCSLSLAPAEGLDFPSGWGLSPQGSVMDERELHPAGTPE  
 PPSSESSLADSSSSWGQEGHFFDLDFLANDPMIPAALLPFQGS~~LIFQVEAVEVTPLSP~~  
 EEEEEEA~~VADPD~~PGGDLAGEGEEDSTSASFLQSLSDLSITEGMDEAFAFRDDTSAASS  
 DSDSASYAEADDERLYSGEPHAQATLLQDSVQKTEEESGGGAKGLQAQDGTVSWAVE  
 AAPQTS~~DRGAYLSQRQELISEVTEEGLALGQESTATVTPHTLQVAPGLQVEVATRVTPQ~~  
 AGEETDSTAGQESAAMAMPQPSQEGISEILGQESVTAEKLP~~TPQEETSLTLC~~PDSPQ

NLKEEGGLDLPSGRKPVAAATIVPRQAKEDLTPQDSAMTPPLPLQDSDLSSAPKPVAA  
 ATIVSQQAE EGLTLPQDSVMTPLPLQDTELSSAPKPVAAATLV SQQAE EGLTLPQDSA  
 MTPPLPLQDSDLSSAPKPVAAATLV SQQAE EGLTLPQDSAMTPPLPLQDSDLSSAPKPV  
 AAATLV SQQAE EGLTLPQDSAMTPPLPLQDSDLSSAPKPVAAATIVSQQAE EGLTLPQD  
 SAMTPPLPLQDSDLSSAPKPVAAATIVSQQAE EGLTLPQDSAMTPPLPLQDSDLSSAPK  
 PVAAATPV SQQAE EGLTLPQDSAMTPPLPLQDSDLSSAPKPVAAATPV SQQAE EGLTL  
 PQDSAMTAPLPLQDTGPTSGPEPLAVATPQTLQAEAGCAPGTEPVATMAQQEVGEAL  
 GPRPAPEEKNAALPTVPEPAALDQVQQDDPQPAEAGTPWAAQEDADSTLGMEALSL  
 PEPASGAGEEIAEALSRPGREACLEARAHTGDGAKPDSPQKETLEVENQQEGGLKLLA  
 QEHGPR SALGGAREVPDAPPAACPEVSQARLLSPAREERGLSGKSTPEPTLPSAVATE  
 ASLDSCPESSVGAVSSLDRGCPDAPAPTSAPTSQQPEPV LGLGSVEQPHEVPSVLGTP  
 LLQPPENLAKGQPSTPVDRPLGPDPSAPGTLAGAALPPLEPPAPCLCQDPQEDSVEDE  
 EPPGSLGLPPPQAGVQPA AA AVSGTTQPLGTGPRVSLSPHSPLLSPKVASMDAKDLAL  
 QILPPCQVPPPSGPQSPAGPQGLSAPEQQEDED SLEEDSPRALGSGQHSDSHGESSA  
 ELDEQDILAPQTVQCPAQAPAGGSEETIAKAKQSRSEKKARKAMSKLGLRQIQGVTRITI  
 QKSKNILFVIAKPDVFKSPASDTYVVFGEAKIEDLSQQVHKAAAEKFKVPSEPSALVPES  
 APRPRVRLECKEEEEEEEEEEVDEAGLELRDIELVMAQANVSRAKAVRALRDNHSDIVNA  
 IMELTM

SEQ ID No:193

MLTTLKPFSGSVSVESKMNNKAGSFFWNLRQFSTLVSTSR TMRLCCLGLCKPKIVHSNW  
 NILNNFHNRMQSTDIIRYLFQDAFIFKSDVGFQTKGISTLTALRIERLLYAKRLFFDSKQSL  
 VPVDKSDDELKKVNLNHEVSNEDVLTKETKPNRISSRKLSEECNSLSDVLD AF SKAPTF  
 PSSNYFTAMWTIAKRLSDDQKRFEKRLMF SHPAFNQLCEHMMREAKIMQYKYLLFSLH  
 AIVKLGIPQNTILVQTLLRVTQERINECDEICLSVLSTVLEAMEPCKNVHVLRTGFRILVDQ  
 QVWKIEDVFTLQVVMKCIGKDAPIALKRKLEMKALRELD RFSVLNSQHMFEVLAAMNHR  
 SLILLDECSKVLDNIHGCP LRIMINILQSCCKDLQYHNLDLFKGLADYVAATFDIWKFRKVL  
 FILILFENLGFRPVGLMDLFMKRIVEDPESLNMKNILSILHTYSSLNHVYKCQNKEQFVEV  
 MASALTGYLHTISSENLLDAVYSFCLMNYFPLAPFNQLLQKDIISELLTSDDMKNAYKLHT  
 LDTCLKLDDTVYLRDIALSLPQLPRELPSSHTNAKVAEVLSSLLGGEGHFSKDVHLPHNY  
 HIDFEIRMDTNRNQVLPLSDVDTT SATDIQRLLTYISFAGLSELKS

SEQ ID No:194

LQLSVKMSVLISQSVINYVEENIPALKALLEKCKDVDERNECGQTPLMIAAEQGNLEIVK  
 ELIKNGANCNLEDLDNWTALISASKEGHVHIVEELLKCGVNLEHRDMGGWTALMWACY  
 KGRTDVVELLLSHGANPSVTGLYSVYPIIWAAGRGHADIVHLLLQNGAKVNCSDKYGTT  
 PLVWAARKGHLECVKHLLAMGADVDDQEGANSMTALIVAVKGGYTQSVKEILKRNPVN  
 LTDKDGNTALMIASKEGHEIVQDLLDAGTYVNIPDRSGDTVIGAVRGGHVEIVRALLQ  
 KYADIDIRGQDNKTALYWAVEKGNATMVRDILQCNPDTEICTKDGETPLIKATKMRNIEV  
 VELLDDKGAKVSAVDKKGDTPLHIAIRGRSRKLAELLRNPKDGRLLYRPNKAGETPYNI  
 DCSHQKSILTQIFGARHLSPTETDGDMLGYDLYSSALADILSEPTMQPPICVGLYAQWG  
 SGKSFLLKKLEDEMKTFAQQIEPLFQFSWLIVFLTLLCGGLGLLFAFTVHPNLGIAVSL  
 SFLALLYIFFIVIYFGGRREGESWNWAWVLSTRLARHIGYLELLLKLMFVNPELPEQTTK  
 ALPVRFLFTDYNRLSSVGGETSLAEMIATLSDACEREFGLATRLFRVFKTEDTQGKKK  
 WKKTCCLPSPFVIFLFIIGCIISGITLLAIFRVDPKHLTVNAVLISIASVVGLAFVLNCRWWQ  
 VLDSLLNSQRKRLHNAASKLHKLKSEGFMKVLKCEVELMARMAKTIDSFTQNTQLRVII  
 DGLDACEQDKVLQMLDTRVFLFSKGPFIASFDPHIIKAINQNLNSVLRDSNINGHDYM  
 RNIVHLPVFLNSRGLSNARKFLVTSATNGDVPCSDTTGIQEDADRRVSQNSLGEMTKLG  
 SKTALNRRDITYRRRQMQRITRQMSFDLTKLLVTEWDFSDISPQTMRRLLNIVSVTGRL  
 LRANQISFNWDRLASWINLTEQWPYRTSWLILYLEETEGIPDQMTLKTIERISKNIPTTK  
 DVEPLLEIDGDIRNFEVFLSSRTPVLVARDVKVFLPCTVNLDPKLREIADVRAAREQISIG  
 GLAYPPLPLHEGPPRAPSGYSQPPSVCSSTSFNGPFAGGVVSPQPHSSYYSGMTGPQ  
 HPFYNRPFAPYLYTPRYYPGGSQHLISRPSVKTS LPRDQNNGLEVIKEDAAEGLSSPT  
 DSSRGSGPAPGPVLLNSLNVDAVCEKQIEGLDQSMPLQYCTTIKKANINGRVLAQC  
 NIDELKKEMNMNFGDWHLFRSTVLEMRNAESHVVPEDPRFLSESSSGPAPHGEPARR  
 ASHNELPHTELSSQTPYTLNFSFEELNTLGLDEGAPRHSNLSWQSQTRRTPSLSSLNS  
 QDSSIEISKLTDKVQAEYRDAYREYIAQMSQLEGGPGSTTISGRSSPHSTYYMGQSSSG  
 GSIHSNLEQEKGKDSEPKPDDGRKSFLMKRGDVIDYSSSGVSTNDASPLDPITEEDEKS  
 DQSGSKLLPGKKSSERSSLFQTDLKLKSGSLRYQKLPSDEDESGTEESDNTPLLKDDK  
 DRKAEGKVERVPKSPEHSAEPIRTFIKAKEYLSDALDKDSSDSGVRSSSESSPNHSLH  
 NEVADDSQLEKANLIELEDDSHSGKRGIPHSLSGLQDPHIIARMSICSEDKKSPSECSLIAS  
 SPEENWPACQKAYNLNRTPTSTVTLNNNSAPANRANQNFDMEGIRETSQVILRPSSSP  
 NPTTIQENENLKSMTHKRSQRSSYTRLSDPPPELHAAASSESTGFGEERESIL

SEQ ID No:195

MGAYLSQPNTVKCSGDGVGAPRLPLPYGFSAMQGWVRVSMEDAHNCIPELDSETAMFS  
 VYDGHGGEEVALYCAKYLDPDIKDQKAYKEGKLQKALEDAFLAIDAKLTTEEVIKELAQIA

GRPTEDEDEKEKVADEDDVDNEEAALLHEEATMTIEELLTRYGQNCHKGPPHSKSGGG  
 TGEPPGSQGLNGEAGPEDSTRETSPQENGPTAKAYTGFSSNSERGTAGQVGEPIG  
 TGEAGPSCSSASDKLPRVAKSKFFEDSEDESDEAEEDSEECSEEDGYSSEEAEEN  
 EEDEDDTEEAEDDEEEEEEMMVPGMEGKEEPGSDSGTTAVVALIRGKQLIVANAGDS  
 RCVVSEAGKALDMSYDHKPEDEVELARIKNAGGKVTMDGRVNGGLNLSRAIGDHFYKR  
 NKNLPPEEQMISALPDIKVLTLTDDHEFMVIACDGIWNVMSSQEVVDFIQSKISQRDENG  
 ELRLSSIVEELLDQCLAPDTSGDGTGCDNMTCHCFKPRNTAELQPESGKRKLEEVLS  
 EGAEENGNSDKKKKAKRD

SEQ ID No:196

MLRMRTAGWARGWCLGCCLLLPLSFLAAAKQLLRYRLAEEGPADVRIGNVASDLGIV  
 TGSGEVTFSLESGSEYKIDNLTGELSTSERRIDREKLPQCQMIFDENECLDFEVSVIG  
 PSQSWVDLFEGQVIVLDINDNTPTFSPVLTLTVEENRPVGTLYLLPTATDRDFGRNGIE  
 RYELLQEPGGGGSGGESRRAGAADSAPYPGGGGNGASGGGSGGSKRRLDASEGGG  
 GTNPGGRSSVFELQVADTPDGEKQPQLIVKGALDREQRDSYELTLRVRDGGDPPRSS  
 QAILRVLITDVNDNSPRFEKSVYEADLAENSAPGTPILQLRAADLDVGVNGQIEYVFGAA  
 TESVRRLRLDETSGWLSVLHRIDREEVNQLRFTVMARDRGQPPKTDKATVVLNIKDEN  
 DNVPSIEIRKIGRIPLKDGVANVAEDVLVDTPIALVQVSDRDQGENGVVTVCTVVGDPVFQ  
 LKPASDTEGDQNKKKYFLHTSTPLDYEATREFNVVIVAVDSGSPSLSSKNSLIVKVGDTN  
 DNPPMFGQSVVEVYFPENNIPGERVATVLATDADSGKNAEIAYSLDSSVMGIFAIDPDS  
 GDILVNTVLDRQTDREYEFKVNADKKGIPVLQGSTTVIVQVADKNDNDPKFMQDVFTFY  
 VKENLQPNSPVGMVTVMADKGRNAEMSLYIEENNNIFSIENTGTIYSTMSFDREHQT  
 TYTFRVKAVDGGDPPRSATATVSLFVMDENDNAPTIVTLPKNISYLLPPSSNVRTTVAT  
 VLATDSDDGINADLNYSIVGGNPFLFEIDPTSGVSLVGKLTQKHVGLHRLVQVND  
 GQPSQSTTTVVHVFNESVSNATAIDSQIARSLHIPLTQDIAGDPSYEISKQRLSIVIGVVA  
 GIMTVILILIVVMARYCRSKNKNNGYEAGKKDHEDFFTPQQHDKSKPKKDKKNKSKQP  
 LYSSIVTVEASKPNGQRYDSVNEKLSDSPSMGRYRSVNGGPGSPDLARHYKSSSPLPT  
 VQLHPQSPTAGKKHQAVQDLPPANTFVGAGDNISIGSDHCSEYSCQTNNKYSKQMLRH  
 PYITVFG

SEQ ID No:197

MEIGWMHNRQRQVLVFFVLLSLSGAGAEELGSYSVVEETERGSFVANLGKDLGLGLTE  
 MSTRKARIISQGNKQHLQLKAQTGDLLINEKLDREELCGPTEPCILHFQVLMENPLEIFQ  
 AELRVIDINDHSPMFTEKEMILKIPENSPLGTEFPLNHALDLVGSNNVQNYKISPSSHFR

VLIHEFRDGRKYPELVLDKELDREEEPQLRLTLTALDGGSPPRSGTAQVRIEVDINDNA  
 PEFEQPIYKVQIPENSPLGSLVATVSARDLDGGANGKISYTLFQPSEDISKTLEVNPMTG  
 EVRLRKQVDFEMVTSYEVRIKATDGGGLSGKCTLLLQVVDVNDNPPQVTMSALTSPIPE  
 NSPEIVVAVFSVSDPDSGNNGKTISSIQEDLPFLLKPSVKNFYTLVTERALDREARAEYNI  
 TLTVTDMGTPRLKTEHNITVQISDVNDNAPTFTQTSYTLFVRENNSPALHIGSVSATDRD  
 SGTNAQVTYSLLPPQDPLPLASLV SINADNGHLFALRSLDYEALQAFEFVRVGATDRGS  
 PALSREALVRVLVLDANDNSPFVLYPLQNGSAPCTELVPRAAEPGYLVTKVVAVDGDS  
 GQNAWLSYQLLKATEPGLFGVWAHNGEVRTARLLSERDAAKQRLVVLVKDNGEPPRS  
 ATATLHVLLVDGFSQPFLPLPEAAPGQTQANSLTVYLVVALASVSSLFLFSVLLFVAVRL  
 CRRSRAASVGRCSMPEGPFPGRLVDVSGTGTLSQSYQYEVCLTGGSETSEFKFLKPIIP  
 NFSP

SEQ ID No:198

MDEDVLTTLKILIIGESGVGKSSLLLRFTDDTFDELAATIGVDFKVKTISVDGNKAKLAIW  
 DTAGQERFRTLTPSYRGAQGVLVYDVTRRDTFVKLDNWLNELETYCTRNDIVNMLVG  
 NKIDKENREVDRNEGLKFARKHSMFLIEASAKTCDGVQCAFEELVEKIIQTPGLWESEN  
 QNKGVKLSHREEGQGGGACGGYCSVL

SEQ ID No:199

MACSIVQFCYFQDLQAARDFLFPHLREEILSGALRRDPSKSTDWEDDGWGAWEENEP  
 QEPEEEGNTCKTQKTSWLQDCVLSLSPTNDLMVIAREQKAVFLVPKWKYSDKGKEEM  
 QFAVGWWSGLNVEEGECVTSALCIPLASQKRSSTGRPDWTCIVVGFTSGYVRFYTENG  
 VLLLAQLLNEDPVLQLKCRTYEIPRHPGVTEQNEELSILYPAAIVTIDGFSLFQSLRACRN  
 QVAKAAASGNENIQPPPLAYKKWGLQDIDTIIDHASVGIMTLSPFDQMKTASNIGGFNAA  
 IKNSPPAMSQYITVGSNPFTGFFYALEGSTQPLLSHVALAVASKLTSALFNAASGWLGW  
 KSKHEEEAVQKQKPKVEPATPLAVRFGLPDSSRRHGESICLSPCNTLAAVTDDFGRVILL  
 DVARGIAIRMWKGYRDAQIGWIQTVEDLHERVPEKADFSPFGNSQGSPSRVAQFLVIYAP  
 RRGILEVWSTQQGPRVGAFNVGKHCRLLYPGYKIMGLNNVTSQSWQPQTYQICLVDPV  
 SGSVKTVNVPFHLALSDKKSERAKDMHLVKKLAALLKTKSPNLDLVETEIKELILDIKYP  
 TKKQALESILASERLPFSCLRNITQTLMDTLKSQELESVDEGLLQFCANKLKLQLYESVS  
 QLNSLDFHLDTPFSDNDLALLRLDEKELLKLQALLEKYKQENTRTNVRFSDDKDGVLP  
 VKTFLEYLEYEKDVLNIKKISEEEYVALGSFFFWKCLHGESSSTEMCHTLESAGLSPQLL  
 LLLLLSVWLSKEKDILDKPQSICCLHTMLSLLSKMKVAIDETWDSQSVSPWWQQMRTA  
 CIQSENNGAALLSAHVGHSAQAQISNNMTEKKFSQTVLGADSEALTDSEALSLDTEY

WKLLLKQLEDCLILQTLLHSGKNTQTSKVSSLQAEPLPRLSVKKLLEGGKGGIADSVAK  
WIFKQDFSPEVLKLANEERDAENPDEPKEGVNRSFLEVSEMEMDLGAIPDLLHLAYEQF  
PCSLELDVLHAHCCWEYVWQWNKDPEEARFFVRSIEHLKQIFNAHVQNGIALMMWNTF  
LVKRFSAAATYLMDKVGKSPKDRLCRRDVGMSDTAMTSFLGSCDLLQILMEADVSRDEI  
QVPVLDTEDAWLSVEGPISIVELALEQKHIHYPLVEHHSILCSILYAVMRFSLKTVKPLSLF  
DSKGKNAFFKDLTSIQLLPSGEMDPNFISVRQQFLLKVVSAAVQAQHSATKVKDPTEEA  
TPTPFGKDQDWPALAVDLAHLQVSEDVRRHYVGELYNYGVDHLGEEAILQVHDKEV  
LASQLLVLTGQRLAHALLHTQTKEGMELLARLPPTLCTWLKAMDPQDLQNTTEVPIATTA  
KLVNKVIELLPEKHGQYGLALHLIEAVEAISLPSL

SEQ ID No:200

MTVSGPGTPEPRPATPGASSVEQLRKEGNELFKCGDYGGALAAYT.QALGLDATPQDQ  
AVLHRNRAACHLKLEDYDKAETEASKAIEKDGGDVKALYRRSQALEKLGRLDQAVLDLQ  
RCVSLEPKNKVFQEALRNIGGQIQEKVRYMSSTD AKVEQMFQILLDPEEKGTEKKQKAS  
QNLVVLAREDAGAIEKIFRSNGVQLLQRLLDMGETDLMLAALRTL VGICSEHQSRVATL  
SILGTRRVVSILGVESQAVSLAACHLLQVMFDALKEGVKKGFRGKEGAIIVDPARELKVLI  
SNLLDLLTEVGVSGQGRDNALTLLIKAVPRKSLKDPNNSLT LWVIDQGLKKILEVGGSLQ  
DPPGELAVTANSRMSASILLSKLFDDLKCDARENFHRLCENYIKSWFEGQGLAGKLRA  
IQTVSCLLQGPCDAGNRALELSGVMESVIALCASEQEEEEQLVAVEALIIHAAGKAKRASFI  
TANGVSLLKDLKYCSEKDSIRIRALVGLCKLGSAGGTDFSMKQFAEGSTLKLAKQCRKW  
LCNDQIDAGTRRWAVEGLAYLTFDADVKEEFVEDAAALKALFQLSRLEERSVLF AVASA  
LVNCTNSYDYEEDPKMV ELAKYAKQHVPEQH PKDKPSFVRARVKKLLAAGVVSAMVC  
MVKTESPVLTS SCRELLSRVFLALVEEVEDRGTVVAQGGGRALIPLALEGTDVGQTKAA  
QALAKLTITSNPEMTFPGERIYEVVRPLVSLHLNCSGLQNF EALMALTNLAGISERLRQ  
KILKEKAVPMIEGYMFEEHEMIRRAATECMCNLAMSKEVQDLFEAQGNDR LKLLVLYSG  
EDDELLQRAAAGGLAMLTSMRPTLCS RIPQVTTHWLEILQALLSSNQELQHRGAVVVL  
NMVEASREIASTLMESEMMEILSVLAKGDHSPVTRAAAACLDKAVEYGLIQPNQDGE

SEQ ID No:201

MSGELPPNINIKEPRWDQSTFIGRANHFFTVTDPRNILLTNEQLESARKIVHDYRQGIVP  
PGLTENELWRAKYIYDSAFHPDTGEKMILIGRMSAQVPMNMTITGCMMTFYRTTPAVLF  
WQWINQSFNNAVNYTNRS GDAPLTVNELGTAYVSATTGAVATALGLNALT KHVSP LIGR  
FVPFAAVAAANCINIPLMRQRELKVGIPVTDENG NRLGESANA AKQAITQVVVSRILMAA

PGMAIPPFIMNTLEKKAFLKRFPWMSAPIQVGLVGFCCLVFATPLCCALFPQKSSMSVTSL  
EAELQAKIQESHPELRRVYFNKGL

SEQ ID No:202

MSQWYELQQLDSEKFLQVHQLYDDSFPMERQYLAQWLEKQDWEHAANDVSFATIRF  
HDLLSQLDDQYSRFSLENNFLLQHNIRKSKRNLQDNFQEDPIQMSMIIYSCLKEERKILE  
NAQRFNQAQSGNIQSTVMLDKQKELDSKVRNVKDKVMCIEHEIKSLEDLQDEYDFKCK  
TLQNRHETNGVAKSDQKQEQLLLKMYLMLDNKRKEVVKHIIELNLTQNALINDE  
LVEWKRRQQSACIGGPPNACLQDQNWFTIVAESLQQVRQQLKKLEEELEQKYTYEHDP  
ITKNKQVLWDRTFSLFQQLIQSSFVVERQPCMPHPQRPLVLKTGVQFTVKLRLLVVKLQ  
ELNYNLKVKVLFDKDVNERNTVKGFRKFNLGTHTKVMNMEESTNGSLAAEFRHLQLKE  
QKNAGTRTNEGPLIVTEELHSLSFETQLCQPGGLVIDLETTSLPVVISNVSQLPSGWASIL  
WYNMLVAEPRNLSFFLTPPCARWAQLSEVLSWQFSSVTKRGLNVDQLNMLGEKLLGP  
NASPDGLIPWTRFCKENINDKNFPFWLWIESILELIKHLPLWNDGCIMGFISKERERAL  
LKDQQPGTFLRFSESSREGAITFTWVERSQNGGEPDFHAVEPYTKKELSAVTFPDIIR  
NYKVMAAENIPENPLKYLYPNIDKDHAFGKYYSRPKEAPEPEMELDGPKGTYIKTELISV  
SEVHPSRLQTTDNLLPMSPEEFDEVSRIVGSVEFDSMMNTV

SEQ ID No:203

MVGEEKMSLRNRLSKSRENPEEDEDQRNPAKESLETSPNGRIDIKQLIAKKIKLTAEAE  
LKPFFMKEVGSFDDFVTNLIEKSASLDNGGCALTTFVLEGEKNNHRAKDLRAPPEQG  
KIFIARRSLDELLEVDHIRTIIYHMFIALILFILSTLVVDYIDEGRLVLEFSLLSYAFGKFPTV  
VWTWWIMFLSTFSVPYFLFQHWATGYSSKSHPLIRSLFHGFLFMIFQIGVLGFGPTYVVL  
AYTLPPASRFIIIFEQIRFVMKAHSFVRENVPRVLNSAKEKSSTVPIPTVNQYLYFLFAPTLI  
YRDSYPRNPTVRWGYVAMKFAQVFGCFYVYIFERLCAPLFRNIKQEPFSARVLVLCV  
FNSILPGVLILFTFFAFLHCWLNAFAEMLRFGDRMFYKDWWNSTSYSNYYRTWNVVV  
HDWLYYYAYKDFLWFFSKRFKSAAMLAVFAVSAVVHEYALAVCLSFYFVFLVLFMFFG  
MAFNFIVNDSRKKPIWNVLMWTSFLGNGVLLCFYSQEWYARRHCPLKNPTFLDYVRP  
RSWTCRYVF

SEQ ID No:204

MKAMDVLPIKKEKVAYLSGGRDKRGGPILTFPARSNHDIRQEDLRRRLISYLACIPSEEV  
CKRGFTVIVDMRGSKWDSIKPLLKILQESFPCCIHVALIKPDNFWQKQRTNFGSSKFEF  
ETNMVSLEGLTKVVDPSQLTPEFDGCLEYNHEEWIEIRVAFEDYISNATHMLSRLEELQ

DILAKKELPQDLEGARNMIEEHSQKKKVIKAPIEDLDLEGQKLLQRIQSSESFPKKNSSGS  
 GNADLQNLLPKVSTMLDRLHSTRQHLHQMWHVRKCLKLDQCFQLRRLFQDAEKMFDWI  
 THNKGLFLNSYTEIGTSHPHAMELQTQHNHFAMNCMVYVNINRIMSVANRLVESGHY  
 ASQQIRQIASQLEQEWKAFAAALDERSTLLDMSSIFHQKAEKYMSNVDSWCKACGEVD  
 LPSELQDLEDAIHQQGIYEHITLAYSEVSQDGKSLLDKLRPLTPGSSDSLTAANYSK  
 AVHHVLDVIHEVLHHQRHVRTIWQHRKVRLHQRLQLCVFQQEVQQVLDWIENHGEAFL  
 SKHTGVGKSLHRARALQKRHEDFEEVAQNTYTNADKLLEAAEQLAQTGECDPEEIYQA  
 AHQLEDRIQDFVRRVEQRKILLDMSVSFHTHVKEWLVLEELQKELLDDVYAESVEAVQ  
 DLIKRFQGGQQTTLQVTNVVIKEGEDLIQQLRDSAISNNKTPHNSSINHIETVLQQLDEAQ  
 SQMEELFQERKIKLELFLHVRIFERDAIDIISDLESWNDELSQQMNDFTEDLTIAEQRLQ  
 HHADKALTMNNLTDFVIHQGDLLQYVNEVQASGVELLCDRDVDMATRVQDLLEFLHE  
 KQQELDLAAEQHRKHLEQCVQLRHLQAEVKQVLGWIRNGESMLNAGLITASSLQEAQ  
 LQREHEQFQHAIEKTHQSALQVQQKAEAMLQANHYDMDMIRDCAEKVASHWQQMLK  
 MEDRLKLVNASVAFYKTSEQVCSVLESLEQEYKREEDWCGGADKLGPNSETHVTPMI  
 SKHLEQKEAFLKACTLARRNADVFLKYLHRNSVNMPGMVTHIKAPEQQVKNILNELFQR  
 ENRVLHYWTMRKRRLDQCQQYVVFERSAKQALEWIHDNGEFYLTSTHTSTGSSIHTQ  
 ELLKEHEEFQITAKQTKERVKLLIQLADGFCEKGHAHAAEIKKCVTAVDKRYRDFSLRME  
 KYRTSLEKALGISSDSNKSSKSLQLDIIPASIPGSEVKLRDAAHELNEEKRSARRKEFIM  
 AELIQTEKAYVRDLRECMDTYLWEMTSGVEEIPPGIVNKELIIFGNMQEIYEFHNNIFLKE  
 LEKYEQLPEDVGHCFTWADKFQMYVTYCKNKPDESTQLILEHAGSYFDEIQQRHGLAN  
 SISSYLIKPVQRITKYQLLLKELLTCCEEGKGEIKDGLEVMLSVPKRANDAMHLSMLEGF  
 DENIESQGELILQESFQVWDPKTLIRKGRERHLFLFEMSLVFSKEVKDSSGRSKYLYKSK  
 LFTSELGVTEHVEGDPCKFALWVGRTPSTDNKIVLKASSIENKQDWIKHIREVIQERTIHL  
 KGALKEPIHIPKTAPATRQKGRRDGEDLDSQGDGSSQPDITISIASRTSQNTLSDKLSG  
 GCELTVIHDFATACNSNELTIRRGQTVEVLERPHDKPDWCLVRTTDRSPAAEGLVPCGS  
 LCIAHSRSSMEMEGIFNHKDSLVSNDASPPASVASLQPHMIGAQQSSPGPKRPGNTL  
 RKWLTSPVRLSSGKADGHVKKLAHKHKSREVRKSADAGSQKSDSDSAATPQDET  
 EERGRNEGLSSGTLSSSSSGMQSCGEEEGEAGADAVPLPPPMAIQQHSLLQPDSDQ  
 DKASSRLLVRPTSSETPSAAELVSAIEELVKSKMALEDPRSSLLVDQGDSSSPSFNPSD  
 NSLLSSSSPIDEMEERKSSSLKRRHYVLQELVETERDYVRDLGYVVEGYMALMKEDGV  
 PDDMKGKDKIVFGNIHQIYDWHRDFFLGELEKCLEDEPEKLGSLFVKHERRLHMYIAYCQ  
 NKPKSEHIVSEYIDTFEDLKQRLGHRQLTDLIKPVQRIMKYQLLLKDFLKYSKKASLD  
 TSELERAVEVMCIVPRRCNDMMNVGRLQGFDGKIVAQGKLLLQDTFLVTDQDAGLLPR  
 CRERRIFLFEQIVIFSEPLDKKKGFSMPGFLFKNSIKVSCLCLEENVENDPCKFALTSRTG

DVETFILHSSSPSVRQTWIHEINQILENQNRNFLNALTSPIEYQRNHSGGGGGGGSGAA  
 AGVGAAAAAGPPVAAAATVAAPAAAAAPPARAGAGPPGSPSLSDTTPPCWSPLQPRA  
 RQRQTRCQSESSSSSNISTMLVTHDYTAVKEDEINVYQGEVVQILASNQQNMFLVFRAA  
 TDQCPAAEGWIPGFVLGHTSAVIVENPDGTLKKSTSWHTALRLRKKSEKKDKDGKREG  
 KLENGYRKSREGLSNKVSVKLLNPNIYDVPPEFVIPLSEVTCETGETVVLRCRVCGRP  
 KASITWKGPEHNTLNNDGHYSISYSIDLGEATLKIVGVTTEDDGIYTCIAVNDMGSSASSA  
 SLRVLGPGMDGIMVTWKDNFDSFYSEVAELGRGRFSVVKCDQKGTKRAVATKQVFNK  
 KLMKRDQVTHELGILQSLQHPLLVGLLDTFETPTSYILVLEMADQGRLLDCVVRWGSLT  
 EGKIRAHLEGEVLEAVRYLHNCRIAHLDLKPENILVDESLAKPTIKLADFGDAVQLNTTYI  
 HQLLGNPEFAAPEIILGNPVSLTSDTWSVGVLTIVLLSGVSPFLDDSVETCLNICRLDF  
 SFPDDYFKGVSQKAKEFVCFLQEDPAKRPSAALALQEQWLQAGNGRSTGVLDTSRLT  
 SFIERRKHQNDVRPIRSIKNFLQSRLLPRV

SEQ ID No:205

MAVFVLLALVAGVLGNEFSILKSPGSVFRNGNWPIPIGERIPDVAALSMGFSVKEDLS  
 WPGLA VG NLFHRPRATVMVMVKG VNK LALPPGSVISYPLENAVPFSLDSVANSIHSLSFS  
 EETPVVLQLAPSEERVYMGKANSVFEDLSVTLRQLRNRLFQENSVLSSLPLNSLSRNN  
 EVDLLFLSELQVLHDISSLSRHKHLAKDHSPDLYSLELAGLDEIGKRYGEDSEQFRDAS  
 KILVDALQKFADDMYSLYGGNAVVELVTVKSFDTSIRKTRTILEAKRAKNPASPYNLAY  
 KYNFEYSVVFNMVLWIMIALALAVIITSYNIWNMDPGYDSIYRMTNQKIRMD

SEQ ID No:206

MNTVLSRANSLFAFSLSVMAALTFGCFITTA FKDRSVPVRLHVSRI MLKNVEDFTGPRER  
 SDLG FITSDITADLENIFDWNVKQLFLYLSAEYSTKNNALNQVVLWDKIVLRGDNPKLLK  
 DMKTKYFFFDGNGLKGNRNVTLTLSWNVVPNAGILPLVTGSGHVSVPFPDYEITKSY

SEQ ID No:207

MGEPA G VAGTME SPFSPGLFHR LDEDWDSALFAELGYFTDTDELQLEAANETYENNFD  
 NLDFDL LLPWESDIWDINNQICTVKDIKAEPQPLSPASSYSVSSPRSVDSYSSTQHVP  
 EEDLSSSSQMSPLSLYGENSNSLS SPEPLKEDK PVTGSRNKTENGLTPKKKIQVNSKP  
 SIQPKPLLLPAAPKTQTNSSVPAKTIIIQTVPTLMPLAKQQPIISLQPAPTKGQTVLLSQPT  
 VVQLQAPGVLP SAQPVLAVAGGV TQLPNHVNVVPAPSANS PVNGKLSVTKPVLQSTM  
 RNVGSDIAVLRRQQRM IKNRESACQSRKKKKEYMLGLEARLKAALSENEQLKKENGTL  
 KRQLDEVVSENQRLKVPSPKRRVVCVMIVLAFIILNYGPM SMLEQDSRRMNPSVGPAN

QRRHLLGFSAKEAQDTSBGIIQKNSYRYDHSVSNDKALMVLTEEPALLYIPPPCQPLINT  
TESLRLNHELRGWVHRHEVERTKSRRMTNNQQKTRILQGVVEQGSNSQLMAVQYTET  
TSSISRNSGSELQVYYASPRSYQDFFFAIRRRGDTFYVVSFRRDHLLLPATTHNKTTRP  
KMSIVLPAININENVINGQDYEVMMQIDCQVMDTRILHIKSSSVPPYLRDQQRNQNTNFF  
GSPPAATEATHVSTIPESLQ

SEQ ID No:208

MTAAVFFGCAFIAGFPALALYVFTIATEPLRIIFLIAGAFFWLVSLLISSLVWFMARVIIDNK  
DGPTQKYLLIFGAFVSVYIQEMFRFAYYKLLKKASEGLKSINPGETAPSMRLLAYVSGLG  
FGIMSGVFSFVNTLSDSLGPGTVGIHGDSPQFFLYSAFMTLVIIILHVFHWGIVFFDGCCEK  
KWGILLIVLLTHLLVSAQTFISSYYGINLASAFIILVLMGTWAFLAAGGSCRSCLKCLLCQD  
KNFL LYNQRSR

SEQ ID No:209

MPLLFLERFPWPSLRTYTGLSGLALLGTIISAYRALSQPEAGPGEPDQLTASLQPEPPAP  
ARPSAGGPRARDVAQYLLSDSLFVWVLVNTACCVLMLVAKLIQCIVFGPLRVSERQHKL  
DKFWNFIFYKFIFIFGVLNVQTVEEVVMWCLWFAGLVFLHLMVQLCKDRFEYLSFSPTTP  
MSSHGRVLSLLVAMLLSCCGLAAVCSITGYTHGMHTLAFMAAESLLVTVRTAHVILRYVI  
HLWDLNHEGTWEGKGTYYTDFVMELTLLSLDLMHHIHMLLFGNIWLSMASLVIFMQL  
RYLFHEVQRRIRRHKNYL RVVGNMEARFAVATPEELAVNNDCAICWDSMQAARKLPC  
GHLFHNSCLRSWLEQDTSCTCRMSLNADNNRVREEHQGENLDENLVPVAAAEGRP  
RLNQHNHFFHFDGSRIASWLPSFSVEVMHTTNILGITQASNSQLNAMAHQIQEMFPQVP  
YHLVLQDLQLTRSVEITTDNILEGRIQVPFPTQRSDSIRPALNSPVERPSSDQEEGETSA  
QTERVPLDLSPRLEETLDFGEVEVEPSEVEDFEARGSRFSKSADERQRMLVQRKDELL  
QQARKRFLNKSSSEDDAASESFLPLEGASSDPVTLRRRMLAAAERRLQKQQT

SEQ ID No:210

MATALSEEELDNEDYYSLNVRREASSEELKAAYRRLCMLYHPDKHRDPELKSQAERL  
FNLVHQAYEVLSDPQTRAIYDIYGKRGLEMEGWVVERRRTPAEIREEFERLQREEREER  
RLQQRTNPKGTISVGVDATDLFDYDEEYEDVSGSSFPQIEINKMHISQSIEAPLTATDT  
AILSGSLSTQNGNGGGSINFALRRVTSAGKWGELEFGAGDLQGPLFGLKLFRNLTPRCF  
VTTNCALQFSSRGIRPGLTTVLARNLDKNTMGYLQWRWGIQSAMNTSIVRDTKTSHFTV  
ALQLGIPHSFALIYQHKFQDDDQTRVKGSLKAGFFGTVVEYGAERKISRHSVLGAAVSV  
GVPQGVSLKVKLNRSQTYFFPIHLTDQLLPSAMFYATVGPLVVYFAMHRLIIPYLRQAQ

KEKELEKQRESAATDVLQKKQEAESAURLMQESVRRRIIEAESRMGLIIVNAWYGKQFVN  
DKSRKSEKVKVIDTVPLQCLVKDSKLILTEASKAGLPGFYDPCVGEENLKVLYQFRGV  
LHQVMVLDSEALRIPKQSHRIDTDG

SEQ ID No:211

MAANYSSSTSTRREHVKVKTSSQPGFLERLSETSGGMFVGLMAFLLSFYLIFTNEGRALK  
TATSLAEGLSLVSPDSIHSVAPENEGRLVHIIGALRTSKLLSDPNYGVHLPVAVKLRRHV  
EMYQWVETEESEYTEDGQVKKETRYSYNTEWRSEIINSKNFDREIGHKNPSAMAVES  
FMATAPFVQIGRFFLSSGLIDKVDNFKSLSLSKLEDPHVDIIRRGDFFYHSENPKYPEVG  
DLRVSFYSYAGLSGDDPDLPAGHVTVIARQRGDQLVPFSTKSGDTLLLLHHGDFSAAEEV  
FHRELRSNSMKTWGLRAAGWMAMFMGLNLMTRILYTLVDWFPVFRDLVNIGLKAF AFC  
VATSLTLLTVAAGWLFYRPLWALLIAGLALVPILVARTRVPAKKLE

SEQ ID No:212

MEDGGLTAFEEDQRCLSQSLPLPVSAEGPAAQTAEPSRSFSSAHRHLSRRNGLSRLC  
QSRTALSEDRWSSYCLSSLAAQNICTSKLHCPAAPEHTDPSEPRGSVSCCSLLRGLSS  
GWSSPLLPAVPCNPKNKAITVDKTTTEILVANDKACGLLGYSSQDLIGQKLTQFFLRSDS  
DVVEALSEEHEADGHAHVVFVGTVDIISRSGEKIPVSVWMKMRQERRLCCVVVLEP  
VERVSTWVAFQSDGTVTSCDSLFAHLHGYVSGEDVAGQHITDLIPSVQLPPSGQHIPKN  
LKIQRSVGRARDGTTFFPLSLKLKSQPSSEEATTGEAAPVSGYRASVWVFCTISGLITLLP  
DGTIHGINHSFALTFLGYGKTELLGKNITFLIPGFYSYMDLAYNSSLQLPDLASCLDVGNE  
SGCGERTLDPWQQQDPAEGGQDPRINVLAGGHVVRDEIRKLMEQDIFTGTQTELI  
AGGQLLSCLSPQPAPGVNDVPEGSLPVHGEQALPKDQQITALGREEPVAIESPGQDLL  
GESRSEPVDPKPFASCEDSEAPVPAEDGGSDAGMCGLCQKAQLERMGVSGPSGSDL  
WAGAAVAKPQAKGQLAGGSLLMHCP CYGSEWGLWWRSDQLAPSPSGMAGLSFGTP  
TLDEPWLGVEN DREELQTCLIKEQLSQLSLAGALDVPHAE LVPTECQAVTAPVSSCDLG  
GRDLCGGCTGSSSACYALATDLPGGLEAVEAQEVDVNSFSWNLKELFFSDQTDQTSS  
NCSCATSELRETPSSLAVGSDPDVGS LQE QGSCVLD DRELLLLTGTCVDLGQGRRFRE  
SCVGHDPTEPLEVCLVSSEHYAASDRSPGHVPSTLDAGPEDTCPSAEPR LN VQVTS  
TPVIVMRGAAGLQREIQEGAYSGSCHHRDGLRLSIQFEVRRVELQGPTPLFCCWL VKD  
LLHSQRDSAARTRLFLASLPGSTHSTAELTGPSLVEVLRARPWFEEPPKAVELEGLAA  
CEGEYSQKYSTMSP LGSGAFGFVWTAVDKEKNKEVVVKFIKKEKVLEDCWIEDPKLGK  
VTLEIAILSRVEHANIIVLDIFENQGGFFQLVMEKHGSGLDLFAFIDRHPRLDEPLASYIFR  
QLVSAVGYLRLKDIIHRDIKDENVIAEDFTIKLIDFGSAAYLERGKLFYTFCGTIEYCAPEV

LMGNPYRGPELEMWSLGVTLTYTLVFEENPFCELEETVEAAIHPPYLVSKELMSLVSGLL  
 QVPERRTTLEKLVTDPWVTQPVNLADYTWEEVCRVKNKPESGVLSAASLEMGNRSLS  
 DVAQAQELCGGPVPGAPNGQGCLHPGDPRLTS

SEQ ID No:213

MVNSSRVQPQQPGDAKRPPAPRAPDPGRLMAGCAAVGASLAAPGRLCEQRGLEIEM  
 QRIRQAAARDPPAGAAASPSPLSSCSRQAWSRDNPGEAEVEVEEGGMVVE  
 MDVEWRPGSRRSAASSAVSSVGARSRLGGYHGAGHPSGRRRRREDQGPPCPSPV  
 GGGDPLHRHLPLEGQPPRVAWAERLVRGLRGLWGTRLMEESSTNREKYLKSVLRELV  
 TYLLFLIVLCILTYGMMSSNVYYYTRMMSQLFLDTPVSKTEKTNFKTLSSMEDFWKFTEG  
 SLLDGLYWKMQPSNQTEADNRSFIFYENLLLGVPRIRQLRVNRNGSCSIPQDLRDEIKEC  
 YDVYSVSSDRAPFGPRNGTAWIYTSEKDLNGSSHWGIIATYSGAGYYLDSRTREETA  
 AQVASLKKNVWLDGRGTRATFIDFSVYNANINLFCVVRLLVEFPATGGVIPSWQFQPLKLI  
 RYVTTDFDFFLAACEIIFCFFIFYVVEEILEIRIHKLHYFRSFWNCLDVVIVVLSVVAIGINIYR  
 TSNVEVLLQFLEDQNTFPNFEHLAYWQIQFNIAAVTVFFVWIKLFKFINFNRTMSQLST  
 TMSRCAKDLFGFAIMFFIIFLAYAQLAYLVFGTQVDDFSTFQECIFTQFRIILGDINFAEIEE  
 ANRVLGPIYFTTFVFFMFFILLNMFLAIINDTYSEVKSDLAQQKAEMELSDLIRKGYHKALV  
 KLKLKKNTVDDISESLRQGGGKLNFDLRLQDLKKGKHTDAEIEAIFTKYDQDGDQELTE  
 HEHQMRDDLEKEREDLDLDHSSLPRPMSSRSFPRSLDDSEEDDDDEDSGHSSRRRG  
 SSSGVSYEEFQVLVRRVDRMEHSIGSIVSKIDAVIVKLEIMERAKLKRREVLGRLLDGVA  
 EDERLGRDSEIHREQMERLVREELERWESDDAASQISHGLGTPVGLNGQPRPRSSRP  
 SSSQSTEGMEGAGGNGSSNVHV

SEQ ID No:214

MEIGWMHNRRQRQVLVFFVLLSLSGAGAEGLSYSVVEETERGSFVANLGKDLGLGLTE  
 MSTRKARIISQGNKQHLQLKAQTGDLLINEKLDREELCGPTEPCILHFQVLNENPLEIFQ  
 AELRVIDINDHSPMFTEKEMILKIPENSPLGTEFPLNHALDLVDGSNNVQNYKISPSSHFR  
 VLIHEFRDGRKYPELVLDKELDREEEPQLRLTLTALDGGSPPRSGTAQVRIEVDINDNA  
 PEFEQPIYKVQIPENSPLGSLVATVSARDLDGGANGKISYTLFQPSDISKTLEVNPMTG  
 EVRLRKQVDFEMVTSYEVRIKATDGGGLSGKCTLLQVVDVNDNPPQVTMSALTSPIPE  
 NSPEIVVAVFSVSDPDSGNNGKTISSIQEDLPFLKPSVKNFYTLVTERALDREARA EYNI  
 TLTVTDMGTPLRKTEHNITVQISDVNDNAPTFTQTSYTLFVRENNSPALHIGSVSATDRD  
 SGTNAQVTYSLLPPQDPLPLASLV SINADNGHLFALRSLDYEALREFEFRVSATDRGS  
 PALSSEALVRVLVDANDNSPFVLYPLQNGSAPCTELVPRAAEPGYLVTKVVAVDGDSG

QNAWLSYQLLKATEPGLFGVWAHNGEVRTARLLSERDAAKQRLVVLVKDNGEPPRSA  
 TATLHVLLVDGFSQPFLPLPEAAPGQQTQANSLTVYLVWALASVSSLFLFSVLLFVAVRLC  
 RRSRAASVGRCSMPEGPFPGRLVDVSGTGTLSSQSYQYEVCLTGGSETSEFKFLKPIIPN  
 FSP

SEQ ID No:215

MVPEAWRSGLVSTGRVGVLLLLGALNKASTVIHYEIPEREKGFVGNVNVANLGLDLG  
 SLSARRFRVSGASRRFFEVRNRETGEMFVNDRDLREELCGTLPSCVTVLELVVENPLEL  
 FSVEVVIQDINDNNPAFPTQEMKLEISEAVAPGTRFPLESAHDPDVGNSLQTYELSRN  
 EYFALRVQTTREDSTKYAELVLERALDREREPSLQLVLTALDGGTPALSASLPIHIKVLDA  
 NDNAPVFNQSLYRARVLEDAPSGTRVQVQLATDLDEGPNGEIIYSFGSHNRAGVRQLF  
 ALDLVTGMLTIKGRDLDFEDTKLHEIYIQAQDKGANPEGAHCKVLVEVVDVNDNAPEITVT  
 SVYSPVPEDAPLGTVIALLSVTDLDAGENGLVTCEVPPGLPFSLTSSLKNYFTLKTSA  
 DRETVPENLSITARDAGTPSLSALTIVRVQVSDINDNPPQSSQSSYDVYIEENNLPGAPI  
 LNLSVWDPDAPQNARLSFFLLEQGAETGLVGRYFTINRDNGIVSSLVPLDYEDRREFEL  
 TAHISDGGTPVLATNISVNIFVTDNRNDNAPQVLYPRPGGSSVEMLPRGTSAGHLVSRVV  
 GWDADAGHNAWLSYSLGSPNQSLFAIGLHTGQISTARPVQDTSRQTLTVLIKDNGE  
 PSLSTTATLTVSVTEDSPEARAEPFSGSAPREQKKNLTFYLLSLILVSVGFVVTVFGVIIF  
 KVKWKQSRDLRAPVSSLYRTPGPSLHADAVRGGLMSPHLYHQVYLTDSRRSDPLL  
 KKPGAASPLASRQNTLRSCDPVFYRQVLGAESAPPGQQAPPNTDWRFSQAQRPQTS  
 GSQNGDDTGTWPNNQFDTEMLQAMILASASEAADGSSTLGGGAGTMGLSARYGPQF  
 TLQHVPDYRQNVYIPGSNATLTNAAGKRDGKAPAGGNGNKKKSGKKEKK

SEQ ID No:216

MCNTPTYCDLGKAAKDVFNKGYGFGMVKIDLKTKSCSGVEFSTSGHAYTDTGKASGNL  
 ETKYKVCNYGLTFTQKWNTDNTLGTEISWENKLAEGLKLTLDITFVPNTGKKSGKLGAS  
 YKRDCFSVGSNVDFSGPTIYGWAVLAFEGWLAGYQMSFDTAKSKLSQNNFALGYKA  
 ADFQLHTHVNDGTEFGGSIYQKVNEKIETSIINLAWTAGSNNTFRGIAAKYMLDCRTSLS  
 AKVNNASLIGLGYTQTLRPGVKLTLSALIDGKNFSAGGHKVGLGFELEA

SEQ ID No:217

MAELMLLSEIADPTRFFTDNLLSPEDWGLQNSTLYSGLDEVAEEQTQLFRCPEDVDPFD  
 GSSLDVGMDVSPSEPPWELLPIFPDLQVKSEPSSPCSSSSLSSESSLSTEPSSEALGV  
 GEVLHVKTESLAPPLCLLGDDPTSSFETVQINVIPTSDDSSDVQTKIEPVSPCSSVNSEA

SLLSADSSSQAFIGEEVLEVKTESLSPSGCLLWDVPAPSLGAVQISMGPSLDGSSGKAL  
PTRKPPLQPKPVVLTTPMPSRAVPPSTTVLLQSLVQPPPVSPPVLIQGAIRVQPEGPAP  
SLPRPERKSIVPAPMPGNSCPPEVDAKLLKRQQRMIKNRESACQSRKKKEYLQGLEA  
RLQAVLADNQQLRRENAALRRRLEALLAENSELKLGSGNRKVCIMVFLLFIAFNFGPVS  
ISEPPSAPISPRMNKGEPQPRRHLLGFSEQEPVQGVEPLQGSSQGPKEPQPSPTDQPS  
FSNLTAFFPGGAKELLLRDLQFLSSDCRHFNRTESLRLADELSGWVQRHQRGRRKIP  
QRAQERQKSQPRKKSPPVKAVPIQPPGPPERDSVGQLQLYRHPDRSQPAFLDAIDRRE  
DTFYVVSFRRDHLLPAISHNKTSRPKMSLVMPAMAPNETLSGRGAPGDYEEMMQIEC  
EVM DTRVHIKTSTVPPSLRKQPSPTPGNATGGPLPVSAASQAHQASHQPLYLNHP

SEQ ID No:218

MTSATSPIILKWDPKSLEIRTLTVERLLEPLVTQVTTLVNTSNKGPSGKKKGRSKKAHVL  
AASVEQATQNFLEKGEQIAKESQDLKEELVAAVEDVRKQGETMRIASSEFADDPCCSSVK  
RGTMVRAARALLSAVTRLLILADMADVMRLLSHLKIVEEAEAVKNATNEQDLANRFKEF  
GKKMVKLNYVAARRQQELKDPHCRDEMAAARGALKKNATMLYTASQAFLRHPDVAAT  
RANRDYVFKQVQEAIAGISNAAQATSPTDEAKGHTGIGELAAALNEFDNKIILDPMTFSE  
ARFRPSLEERLESIIISGAALMADSSCTRRDRRERIVAECNAVRQALQDLLSEYMNNTGR  
KEKGDPLNIAIDKMTKKTRDLRRQLRKAVMDHISDSFLETNVPLLVLIEAAKSGNEKEVK  
EYAQVFREHANKLVEVANLACSSISNNEEGVKLVMAATQIDSLCPQVINAALTAAARPQS  
KVAQDNMDVFKDQWEKQVRVLTEAVDDITSVDDFLSVSENHILEDVNKCVIALQEGDVD  
TLDRTAGAIRGRAARVIHIINAEMENYEAGVYTEKVLEATKLLSETVMPRFAEQVEVAIEA  
LSANVPQPFEENE FIDASRLVYDGVRDIRKAVLMIRTPEELEDSDFEQEDYDVRRGTS  
VQTEDDQLIAGQSARAIMAQLPQEEKAKIAEQVEIFHQEKSCLDAEVAKWDDSGNDIIVL  
AKQMCMIMMEMTDFTRGKGPLKNTSDVINAACKIAEAGSRMDKLARAVADQCPDSACK  
QDLLAYLQRIALYCHQLNICKVKAQVQNLGGELIVSGTGVQSTFTTFYEVD CDVIDGGR  
ASQLSTHLPTCAEGAPIGSGSSDSSMLDSATSLIAAKNLMAVVLTVKASYVASTKYQ  
KVYGTAAVNSPVVSWKMKAPKPLVKREKPEEFQTRVRRGSQKKHISPVQALSEFKA  
MDSF

SEQ ID No:219

MAAQCVTKVALNVSCANLLDKDIGSKSDPLCVLFLNTSGQQWYEVERTERIKNCLNPQF  
SKTFIIDYYFEVVQKLKFGVYDIDNKTIELSDDD FLGEC ECTLGQIVSSKKLTRPLVMKTG  
RPAGKGSITISAEIEKDNRVVLFEMEARKLDNKLDFGKSDPYLEFHKQTS DGNWLMVHR  
TEVVKNNLNPVWRPFKISLNSLCYGDMDKTIKVECYDYDNDGSHDLIGTFQTTMTKLKE

ASRSSPVEFECINEKKRQKKKSYKNSGVISVKQCEITVECTFLDYIMGGCQLNFTVGVD  
 TGSNGDPRSPDSLHYISPNGVNEYLTALWSVGLVIQDYDADKMFFAFGFGAQIPQWQ  
 VSHEFPMNPNPSNPYCNGIQGIVEAYRSCLPQIKLYGPTNFSPIINHVARFAAAATQQQT  
 ASQYFVLLIITDGVITDLDETRQAIVNASRLPMSIIIVGVGGADFSAMEFLDGDGGSRLSPL  
 GEVAIRDIVQFVPFRQFQNAPEALAQCVLAEIPQQVVGYFNTYKLLPPKNPATKQQKQ

SEQ ID No:220

MAVSASPVISATSSGAGVPGGLFRAEPLYSTPREPPRLTPNMINSFVNNHSNSAGGG  
 GRGNTNTNECRMVDMHGMKVASFLMDGQELICLPQVFDLFLKHLVGGLHTVYTKLKRL  
 DISPVVCTVEQVRILRGLGAIQPGVNRCKLITRKDFETLFTDCTNARRKRQMTRKQAVN  
 SSRPGRPPKRSRLGVLQENARLLTHAVPGLLSPGLITPTGITAAAMAEAMKLQKMKLMAM  
 NTLQGNGSQNGTESEPDDLNSNTGGSESSWDKDKMQSPFAAPGPQHGIHAALAGQ  
 PGIGGAPT LNPLQQNHLLTNRLDLPFMMMPHPLLPVSLPPASVAMAMNQMNHLNTIAN  
 MAAAQIHSPLSRAGTSVIKERIPESPSPAPSLEENHRPGSQTSSHTSSSVSSSPSQMD  
 HHLERMEEVPVQIPIMKSPLDKIQLTPGQALPAGFPGFIFADSLSSVETLLTNIQGLLKV  
 ALDNARIQEKQIQQEKELRLELYREREIRENLERQLAVELQSRTTMQKRLKKEKTKRK  
 LQEALFESKRREQVEQALKQATTSDSGLRMLKDTGIPDIEIENNGTPHDSAAMQGGNY  
 YCLEMAQQLYSA

SEQ ID No:221

MACPALGLEALQPLQPEPPPEPAFSEAQKWIEQVTGRSFGDKDFRTGLENGILLCELLN  
 AIKPGLVKKINRLPTPIAGLDNIILFLRGCKELGLKESQLFDPSDLQDTSNRVTVKSLDYSR  
 KLKNVLVTIYWLGAANSCTSYSGTTLNLKEFEGLLAQMRKDTDDIESPKRSIRDSGYID  
 CWDSESRDSLSPPRHGRDDSFDSLDSFGSRSRQTPSPDVVLRGSSDGRGSDSESDLP  
 HRKLPDVKKDDMSARRTSHGEPKSAVPFNQYLPNKSNTAYVPAPLRKKKAEREEYR  
 KSWSTATSPLGGERPFRYGPRTPVSDDAESTSMFDMRCEEEAAVQPHSRARQEQLQL  
 INNQLREEDDKWQDDLARWKSRRRSVSQDLIKKEEERKKMEKLLAGEDGTSERRKSIK  
 TYREIVQEKERRERELHEAYKNARSQEEAEGILQQYIERFTISEAVLERLEMPKILERSHS  
 TEPNLSSFLNDPNPMKYLRQQSLPPPKFTATVETTIARASVLDTSMSAGSGSPSKTVTP  
 KAVPMLTPPKPYSQPKNSQDVLKTFKVDGKVSVNGETVHREEEKERECPVAPAHSLTK  
 SQMFEGVARVHGSPLELKQDNGSIEINIKKPNSVPQELAAATTEKTEPNSQEDKNDGGKS  
 RKGNIELASSEPHFTTTVTRCSPTVAFVEFPSSPQLKNDVSEEKDKKPKPENEMSGKV  
 ELVLSQKVVKPKSPEPEATLTFPFLDKMPEANQLHLPNLNSQVDSPPSSEKSPVMTPFKF  
 WAWDPEEERRRQEKWQQEQERLLQERYQKEQDKLKEEWEKAQKEVEEEEERRYYEE

ERKIIEDTVVPFTVSSSSADQLSTSSSMTEGSGTMNKIDLGNCQDEKQDRRWKKSFGG  
DDSDLLLKTRESRLEEKGSLTEGALAHSGNPVSKGVHEDHQLDTEAGAPHCGTNPQL  
AQDPSQNNQTSNPTHSSSEVDKPKTLPLDKSINHQIESPSERRKKS PREHFQAGPFSPC  
SPTPPGQSPNRSISGKKLCSSCGLPLGKGAAMIETLNLYFHIQCFRCGICKGQLGDAVS  
GTDVIRIRNGLLNCNDCYMRSR SAGQP TTL

SEQ ID No:222

MAARGRRAEPQGREAPGPAGGGGGGSRWAESGSGTSPESGDEEVSGAGSSPVSGG  
VNLFANDGSFLELFKRKMEEEQRQRQEPPPGPQRPDQSAAGPGDPKRKGGPGS  
TLSFVGKRRGGNKLALKTGIVAKKQKTEDEVLT SKGDAWAKYMAEVKKYKAHQCGDD  
DKTRPLVK

SEQ ID No:223

MAAETQTLNFGPEWLRALSSGGSITSPPLSPALPKYKLADYRYGREEMLALFLKDNKIP  
SDLLDKEFLPILQEEPLPPLALVPFTEEEQRNFSMSVNSAAVLRLTGRGGGGTVVGAPR  
GRSSSRGRGRGRGECGFYQRSFDEVEGVFGRGGG REMHRSQSWEERGDRRFEKP  
GRKDVGRPNFEEGGPTSVGRKHEFIRSESENWRIFREEQNGEDEDGGWRLAGSRRD  
GERWRPHSPDGPRSAGWREHMERRRRFEFDFRDRDDERGYRRVRSGSGSIDDDR  
SLPEWCLEDAEEEMGTFDSSGAFLSLKKVQKEPIPEEQEMDFRPVDEGEECSDSEGSH  
NEEAKEPDKTNKKEGEKTD RVGVEASEETPQTSSSSARPGTPSDHQSQEASQFERKD  
EPKTEQTEKAE EETRMENSLPAKVPSRGDEMADVQQPLSQIPSDTASPLLILPPPVPN  
PSPTLRPVETPVVGAPGMGSVSTEPDDEEGLKHLEQQA EKMVAYLQDSALDDERLASK  
LQEHRAKGVSIPLMHEAMQKWYYKDPQGEIQGP FNNQEMA EWFAQYFTMSLLVKRA  
CDES FQPLGDIMKMWGRVPFSPGPAPPPHMGELDQERLTRQQELTALYQM QHLQYQ  
QFLIQQQYAQVLAQQQKAALSSQQQQQLALLLQQFQTLKMRISDQNIIPSVTRSVSPD  
TGSIWELQPTASQPTVWEGGSVWDLPLDTTTPGPALEQLQQL EKAKAAKLEQERREAE  
MRAKREEEERKRQEELRRQQEEILRRQQEEERKRREEEELARRKQEEALRRQREQEIA  
LRRQREEEERQQQEEALRRLEERRREEEERKRQEELLRKQEEEA AWAREEEEEAQRR  
LEENRLRMEEEAARLRHEEEERKRKELEVQRQKELMRQRQQQQEALRRLQQQQQQQ  
QLAQMKLPSSSTWGQQSNTTACQSQATLSLAEIQKLEEEERERQLREEQRRRQRELK  
ALQQQQQQQQQKLSGWGNVSKPSGTTKSLLEIQQEEARQM QKQQQQQQHQQPNR  
ARNNTHSNLHTSIGNSVWGSINTGPPNQWASDLVSSIWSNADTKNSNMGFWD DAVKE  
VGPRNSTNKNKKELK

SEQ ID No:224

MVGKCLKQNLLACLVISSVTVFYLGQHAMECHHRIEERSQPVKLESTRTTVRTGLDLKA  
NKT FayHKDMPLIFIGGVPRSGTTLMRAMLDAHPDIRCGEETRVIPRILALKQMWSRSSK  
EKIRLDEAGVTDEVLDSAMQAFLEIIVKHGEPAPYLCNKDPFALKSLTYLSRLFPNAKFL  
LMVRDGRASVHSMISRKVTIAGFDLNSYRDCLTKWNRAIETMYNQCMVEVGYKKCMLVH  
YEQLVLHPERWMRTLLKFLQIPWNHSLVHHEEMIGKAGGVSLSKVERSTDQVIKPVNV  
GALSKWVGKIPPDVLQDMAVIAPMLAKLGYDPYANPPNYGKPDPKIIENTRRVYKGEFQ  
LPDFLKEKPQTEQVE

SEQ ID No:225

MSTFRQEDVEDHYEMGEELGSGQFAIVRKCRQKGTGKEYAAKFIKKRRLSSSRRGVSR  
EEIEREVNIREIRHPNIITLHDIFENKTDVVLILELVSGGELFDFLAEKESLDEATQFLK  
QILDGVHYLHASKRIAHDLDKPENIMLLDKNVPNPRIKLIDFGIAHKIEAGNEFKNIFGTPEF  
VAPEIVNYEPLGLEADMWSIGVITYILLSGASPFLGETKQETLTNISAVNYDFDEEYFSNT  
SELAKFIRRLLVKDPKRRMTIAQSLEHSWIKAIRRRNVRGEDSGRKPERRRLKTTRLKE  
YTIKSHSSLPPNNSYADFERFSKVL EEA AAAAEEGLRELQRSRRLCHEDVEALAAIYEEKE  
AWYREESDSLQDLRRLRQELLKTEALKRQAQEEAKGALLGTSGLKRRFSRLENRYEA  
LAKQVASEMRVQDLVRALEQEKLGVECGLR

SEQ ID No:226

MAFRQALQLAACGLAGGSAAVLFSAVAVGKPRAGGDAEPRPAEPPAWAGGARPGPG  
VWDPNWDRREPLSLINVRKRNVESGEEELASKLDHYKAKATRHIFLIRHSQYHVDGSLE  
KDRTLTPLGREQAELTGLRLASLGLKFNKIVHSSMTRAIETTDIISRHLPGVCKVSTDLLR  
EGAPIEPDPPVSHWKPEAVQYYEDGARIEAAFRNYIHRADARQEEDSYEIFICHANVIRYI  
VCSIPPLLSAGDFVVLGS

SEQ ID No:227

MSEDNRPLTGLAAAAGAKLRKVS RMEDTSFPSSGGNAIGVNSASSKTD TGRGNGPLPL  
GGSGLMEEMSALLARRRRRIA EKGSTIETE QKEDKGEDSEPVT SKASTSTPEPTRKPW  
ERTNTMNGSKSPVISRPKSTPLSQPSANGVQTEGLDYDRLKQDILDEMRELTKLKEELI  
DAIRQELSKSNTA

SEQ ID No:228

RHTRTHRDTRHTYTHAHTDAHTCTHMRDQTQMHTHTICRKKYALTNIQAAMGLSDPAA  
 QPLLGNNGSANIKLVKNGENQLRKAAEQGQDPNKNLSPTAVINITSEKLEGKEPHQDS  
 SSCEILPSQPRRTKSFLNYYADLETSARELEQNRGNHHGTAEKESQPVQGGQASTIIGNG  
 DLLLQKPNRPQSSPEDGQVATVSSSPETKKDHPKTGAKTDCALHRIQNLAPSDEESSW  
 TTLSQDSASPSSPDETDIWSDFSQTDPDLPPGWKRVSDIAGTYWHIPTGTTQWERP  
 VSIPADLQGSRKSLSSVTPSPTPENKQPWSDFAVLNGGKINSIDIWDLHAATVNPDP  
 SLKEFEGATLRYASLKLNRNAPHPDDDDSCSINSIDPEAKCFAVRSLGWVEMAEEDLAPG  
 KSSVAVNNCIRQLSYCKNDIRDTVGIWGEGKDMYLILENDMLSLVDPMDRSVWHSQPIV  
 SIRVWGVGRDNGRDFAYVARDKDTRILKCHVFRCDTPAKAIATSLHEICSKIMAERKNAK  
 ALACSSLQERANVNLDVPLQVDFPTPKTEL VQKFHVQYLGMLPVDKPVGMDILNSAIEN  
 LMTSSNKEDWLSVNMMNVADATVTVISEKNEEEVLVECRVRFLSFMGVGKDVHTFAFIM  
 DTGNQRFECVFWCEPNAGNVSEAVQAACMLRYQKCLVARPPSQKVRPPPPPADSV  
 TRRVTTNVKRGVLSLIDTLKQKRPVTEMP

SEQ ID No:229

MAERESGGLGGGAASPPAASPFLGLHIASPPNFRLTHTDISLEEFEDDLSEITDECGISL  
 QCKDTLSLRPPRAGLLSAGGGGAGSRLQAEMQLMDLIDATGDTPGAEDDEEDDDEER  
 AARRPGAGPPKAESGQEPASRGQGQSQGQSGGSGDTPRKRPTTLNLFPQVPRS  
 QDTLNNNSLGKKHSWQDRVSRSSSPLKTGEQTPPHEHICLSDELPPQSGPAPTDRGT  
 STDSPCRRSTATQMAPPGGPPAAPPGGRGHSHRDRIHYQADVRLATEEIIYLTVPQRP  
 PDAAEPTSAFLPPTESRMSVSSDPDPAAYPSTAGRPHPSISEEEEEGFDCLSPPERAEPP  
 GGGWRGSLGEPPPPPRASLSSDTSALSYDSVKYTLVVDEHAQLELVSLRPCFGDYSDE  
 SDSATVYDNCASVSSPYESAIGEEYEEAPRPQPPACLSDESTPDEPDVHFSKKFLNVF  
 MSGRSRSSSAESFGLFSCIINGEEQEQTTHRAIFRFVPRHEDELELEVDDPLLVELQAED  
 YWYEAYNMRTGARGVFPAYYAEVTKPEPEHMAALAKNSDWVDQFRVKFLGSVQVPYH  
 KGNDVLCAMQKIATTRRLTVHFNPPSSCVLEISVRGVKIGVKADDSQEAKGNKCSHFF  
 QLKNISFCGYHPKNNKYFGFITKHPADHRFACHVFSVSEDSTKALAESVGRAFQQFYKQF  
 VEYTCPTEDIYLE

SEQ ID No:230

GSELETAMETLINVFHAHSGKEGDYKLSKKELKELLQTELSGFLDAQKDVAVDKVMK  
 ELDENGDEGEVDFQEYVVLVAALTVACNNFFWENS

SEQ ID No:231

SELEKAMVALIDVFHQYSGREGDKHKLKSELKELINNELSHFLEEIKEQEVDKVMETL  
DNDGDGECDFQEFMAFVAMVTTACHEFFEHE

SEQ ID No:232

MLPGLALLLLAAWTARALEVPTDGNAGLLAEPQIAMFCGRLNMHMNVQNGKWSDPS  
GKTCIDTKEGILQYCQEVYPELQITNVVEANQPVTIQNWCKRGRKQCKTHPHFVIPYR  
CLVGEFVSDALLVPDKCKFLHQERMDVCETHLHWHTVAKETCSEKSTNLHDYGMLLPC  
GIDKFRGVFVCCPLAEESDNVDSADAEEDSDVWWGGADTDYADGSEDKVVEVAEE  
EEVAEEVEEEEADDDDEDEDGDEVEEEAEOPYEEATERTTSIATTTTTTTTESVEEVVRP  
TTAASPDAVDKYLETPGDENEHAHFQKAKERLEAKHRERMSQVMREWEEAERQAKN  
LPKADKKAIVQHFQEKVESLEQEAANERQQLVETHMARVEAMLNDRRLALENYITALQ  
AVPPRPRHVFNMLKKYVRAEQKDRQHTLKHFEHVRMVDPKKAAQIRSQVMTHLRVIYE  
RMNQSLSLLYNVPAAVEEIQDEVELLQKEQNYSDDLANMISEPRISYGNDALMPSLT  
ETKTTVELLPVNGEFSLDDLQPWHSFGADSVANTENEVEPVDARPAADRGLTTRPGS  
GLTNIKTEEISEVNLDAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIATVIV  
ITLVMLKKKQYTSIHGVEVDAAVTPEERHLSKMQQNGYENPTYKFFEQMQN

SEQ ID No:233

MTATEALLRVLLLLLAFGHSTYGAECFPACNPQNGFCEDDNVCRCQPGWQGGLCDQC  
VTSPGCLHGLCGEPGQCICTDGWDGELCDRDRACSSAPCANNGTCVSLDGGLYECS  
CAPGYSGKDCQKKDGPCVINGSPCQHGGTCVDDEGRASHASCLCPPGFSGNFCEIVA  
NSCTPNPCENDGVCTDIGGDFRCRCPAGFIDKTCRPVTNCASSPCQNGGTCLQHTQ  
VSYECLCKPEFTGLTCVKKRALSPQQVTRLPSGYGLAYRLTPGVHELPPVQQPEHRILKV  
SMKELNKKTPLLTEGQAICFTILGVLTSLVVLGTGVIVFLNKCETWVSNLRYNHMLRKKK  
NLLLQYNSGEDLAVNIIFPEKIDMTTFSKEAGDEEI

SEQ ID No:234

MVNYAWAGRSQRKLWWRSAVLTC<sup>1</sup>SVVRPGYRGGLQARRSTLLKTCARARATAPG  
AMKMPVAPWTRFYSNSCCLCCHVRTGTILLGVWYLIINAVVLLILLSALADPDQYNFSSSE  
LGGDFEFMDDANMCIAIAISLLMILICAMATYGAYKQRAAWIIPFFCYQIFDFALNMLVAIT  
VLIYPNSIQEYIRQLPPNFPYRDDVMSVNPTCLVLIILLFISIILTFKGYLISCVWNCYRYING  
RNSSDVLVYVTSNDTTVLLPPYDDATVNGAAKEPPPPYVSA

SEQ ID No:235

MATIPDWKLQLLARRRQEEASVRGREKAERERLSQMPAWKRGLLERRRAKLGLSPGE  
PSPVLGTVEAGPPDPDESAVLLEAIGPVHQNRFFIRQERQQQQQQQQRSEELLAERKPG  
PLEARERRPSPGEMRDQSPKGRESREERLSPRETRERRLGIGGAQELSLRPLEARDW  
RQSPGEVGRSSRLSEAWKWRLSPGETPERSLRLAESREQSPRRKEVESRLSPGESA  
YQKLGLTEAHKWRPDSRESQEQLVQLEATEWRLRSGEERQDYSEECGRKEEWPVP  
GVAPKETAELSETLTREAQGNSSAGVEAAEQRPVEDGERGMKPTEGWKWTLNSGKA  
REWTPRDIEAQTQKLEPPESAELLESPPGVEAGEGEAEKEEAGAQRPLRALQNCCSV  
PSPLPPEDAGTGGLRQQEEEAVELQPPPPAPLSPPPPAPTAPQPPGDPLMSRLFYGVK  
AGPGVGAPRRSGHTFTVNPRRSVPPATPATPTSPATVDAAVPGAGKKRYPTAEELVL  
GGYLRLSRSLAKGSPERHHKQLKISFSETALETQYQPSSESSVLEELGPEPEVPSAPN  
PPAAQPDDEEDEEELLLLQPELQGGLRTKALIVDESCRR

SEQ ID No:236

MSEHVEPAAPGPGPNGGGGGPAPARGPRTPNLNPPLINVRDRLFHALFFKMAVTYS  
RLFPPAFRRLFEFFVLLKALFVLFVLAYIHIVFSRSPINCLEHVRDKWPREGILRVEVRHN  
SSRAPVFLQFCDSGGRGSFPGLAVEPGSNLDMEDEEEEELTMEMFGNSSIKFELDIEP  
KVFKPPSSTEALNDSQEFPFPETPTKVWPQDEYIVEYSLEYGFLRLSQATRQRLSIPVM  
VVTLDPTRDQCFGDRFSRLLLDDEFLGYDDILMSSSVKGLAENEENKGFLRNVVSGEHYRF  
VSMWMARTSYLAFAIMVIFTLSVSMMLLRYSHHQIFVFIVDLLQMLEMNMAIAFPAAPLLT  
VILALVGMEAIMSEFFNDTTTAFYIILIVWLADQYDAICCHTSTSKRHWLRRFFLYHFAYFA  
YHYRFNGQYSSALVTSWLFIQHSMIYFFHHYELPAILQQVRIQEMLLQAPPLGPGTPTA  
LPDDMNNNSGAPATAPDSAGQPPALGPVFELVSKERGWGSAEGSGGVLVGLQ

SEQ ID No:237

KEQSELDQDLDDVEEVEEEEETGEETKLKARQLTVQMMQNPQILAALQERLDGLVETPT  
GYIESLPRVVKRRVNALKNLQVKCAQIEAKFYEEVHDLERKYAVLYQPLFDKRFEIINAIY  
EPTEECEWKPDDEDEISEELKEKAKIEDEKKDEEKEDPKGIPEFWLTVFKNVDLLSDM  
VQEHDEPILKHLKDIKVKFSDAGQPMFVLEFHFEPNEYFTNEVLTKTYRMRSEPDDSD  
PFSFDGPEIMGCTGCQIDWKKGKNVTLKTIKKKQKHKGRTVTVTKTVSNDSSFFNFFA  
PPEVIPKFSAFDDDAEAILAADFEIGHFLRERIIPRSVLYFTGEAIEDDDDDYDEEGEEAD  
EGYQLFEEVKSCSKLFQRWLQ

SEQ ID No:238

GKQNSKLRPEVMQDLLESTDFTEHEIQEWYKGFLRDCPSGHLSMEEFKKIYGNFFPYG  
 DASKFAEHVFRFTDANGDGTIDFREFIIALSVTSRGKLEQKLKWAFSMYDLGNGYISKA  
 EMLEIVQAIYKMVSSVMKMPPEDESTPEKRTEKIFRQMDTNRDGKLSLEEFIRGAKSDPSI  
 VRLLQCDPSSAGQF

SEQ ID No:239

MVEKGPEVSGKRRGRNNAASASAAAAASAAASAACASPAATAASGAAASSASAAAAAS  
 AAAAPNNGQNKSLAAAAPNGNSSSNSWEEGSSGSSSDEEHGGGGMRVGPQYQAVV  
 PDFDPAKLARRSQERDNLGMLVWSPNQNLSEAKLDEYIAIAKEKHGYNMEQALGMLFW  
 HKHNIKSLADLPNFTFPDEWTVEDKVLFEQAFSFGKTFHRIQQMLPDKSIASLVKFY  
 YSWKKTRTKTSVMDRHARKQKREREESEDELEEANGNNPIDIEVDQNKESKKEVPTE  
 TVPQVKKEKHSTQAKNRAKRKPPKGMFLSQEDVEAVSANATAATTVLRLQDMELVSVK  
 RQIQNIKQTNALKEKLDGGIEPYRLPEVIQKCNARWTTEEQLLAVQAIRKYGRDFQAIS  
 DVIGNKSVVQVKNFFVNYRRRFNIDEVLQEWEAEHGKEETNGPSNQKPKVSPDNSIKM  
 PEEDEAPVLDVRYASAS

SEQ ID No:240

MDDDIAALVVDNGSGMCKAGFAGDDAPRAVFPSIVGRPRHQGVMVGMGQKDSYVGD  
 EAQSKRGILTLYPIEHGIVTNWDDMEKIWHHTFYNELRVAPEEHPVLLTEAPLNPKANR  
 EKMTQIMFETFNTPAMYVAIQAVLSLYASGRTTGIVMDSGDGVTHTVPIYEGYALPHAIL  
 RLDLAGRDLTDYLMKILTERGYSFTTTAEREIVRDIKEKLCYVALDFEQEMATAASSSSL  
 EKSVELPDGQVITIGNERFRCPEALFQPSFLGMESCGIHETTFNSIMKCDVDIRKDLNAN  
 TVLSGGTTMYPGIADRMQKEITALAPSTMKIKIIPPERKYSVWIGGSILASLSTFQQMWI  
 SKQEYDESGPSIVHRKCF

SEQ ID No:241

MRECISIHVGQAGVQIGNACWELCYCLEHGIQPDGQMPSDKTIGGGDDSFNTFFSETGA  
 GKHVPRAVFVDLEPTVIDEVRTGTYRQLFHPEQLITGKEDAANNYARGHYTIGKEIIDLVL  
 DRIRKLADQCTGLQGFLVFHSFGGGTGSGFTSLLMERLSVDYGKKSLEFSIYPAPQVS  
 TAVVEPYNSILTTHTTLEHSDCAFMVDNEAIYDICRRNLDIERPTYTNLNLISQIVSSITA  
 SLRFDGALNVDLTFQTNLVPYPRIHFPLATYAPVISAEKAYHEQLSVAEITNACFEPAN  
 QMVKCDPRHKGKYMCCLLYRGDVVPKVDNAAIATIKTKRSIQFVDWCPTGFKVGINYQ  
 PPTVPPGGDLAKVQRAVCMLSNTTAIAEAWARLDHKFDLMYAKRAVHVHWYVGEEMEE  
 GEFSEAREDMAALEKDYEYEEVGVDSVEGEGEEEEGEEY

SEQ ID No:242

MREIVHIQAGQCGNQIGAKFWEVISDEHGIDPTGTYHGSDQLQDRISVYYNEATGGKY  
 VPRAILVDLEPGTMDSVRSGPFGQIFRPDNFVFGQSGAGNNWAKGHYTEGAELVDSVL  
 DVVRKEAESCDCLQGFQLTHSLGGGTGSGMGTLLISKIREEYPDRIMNTFSVVPSPKVS  
 DTVVEPYNATLSVHQLVENTDETYCIDNEALYDICFRTLKLTTPTYGDLNHLVSATMSGV  
 TTCLRFPGQLNADLRKLAVNMVPPRLHFFMPGFAPLTSRGSQQYRALTVPELTQQVF  
 DAKNMMAACDPRHGRYLTVAAVFRGRMSMKEVDEQMLNVQKNSSYFVEWIPNNVK  
 TAVCDIPPRGLKMAVTFIGNSTAIQELFKRISEQFTAMFRRKAFLHWYTGEGMDEMEFT  
 EAESNMNDLVSEYQQYQDATAEEEEEDFGEEAEAAA

SEQ ID No:243

MEGSLEREAPAGALAAVLKHSSTLPPESTQVRGYDFNRGVNYRALLEAFGTTGFQATN  
 FGRAVQQVNAMEIEKKLEPLSQDEDDQHADLTQSRRLTSCTIFLGYTSNLISSGIRETIRYL  
 VQHNMDVLDVTTAGGVEEDLIKCLAPTYLGEFSLRGKELRENGINRIGNLLVPNENYCKF  
 EDWLMPILDQMVMEQNTEGVKWTPSKMIARLGKEINNPEVYWAQKNHIPVFSPALT  
 DGSLGDMIFFHSYKNPGLVLDIVEDLRLINTQAIFAKCTGMILGGGVVKHHIANANLMRN  
 GADYAVYINTAQEFDGSDSGARPDEAVSWGKIRVDAQPVKVYADASLVFPLLVAETFA  
 QKMDAFMHEKNED

SEQ ID No:244

MADPKYADLPGIARNEPDVYETSDLPEDDQAEFDAEELTSTSVEHIIVNPNAAYDKFKDK  
 RVGTKGLDFSDRIGKTKRTGYESGEYEMLGEGLGVKETPQQKYQRLLHEVQELTTEVE  
 KIKTTVKESATEEKLTPVLLAKQLAALKQQLVASHLEKLLGPDAAINLTDPDGALAKRLLL  
 QLEATKNSKGGSGGKTTGTPDSSLVTYELHSRPEQDKFSQAAKVAELEKRLTELETA  
 VRCDQDAQNPLSAGLQGACLMETVELLQAKVSALDLAVLDQVEARLQSVLGKVNEIAK  
 HKASVEDADTQSKVHQLYETIQRWSPIASTLPELVQRLVTIKQLHEQAMQFGQLLTHLD  
 TTQQMIANSLKDNTLLTQVQTTMRENLATVEGNFASIDERMKKLGK

SEQ ID No:245

MRKETPPPLVPPAAREWNLPNAPACMERQLEAARYRSDGALLLGASSLSGRCWAGS  
 LWLFKDPCAAAPNEGFCASAGVQTEAGVADLTWVGGERGILVASDSGAVELWELDENETLI  
 VSKFCKYEHDDIVSTVSVLSSGTQAVSGSKDICIKVWDLAQQVVLSSYRAHAAQVTCVA  
 ASPHKDSVFLSCSEDNRILLWDTRCPKPASQIGCSAPGYLPTSLAWHPQQSEVFVFGD

ENGTVSLVDTKSTSCVLSSAVHSQCVTGLVFSPHSVPFLASLSEDCSLAVLDSSLSELF  
RSQAHRDFVRDATWSPLNHSLTTVGWDHQVVHHVVPTEPLPAPGPASVTE

SEQ ID No:246

MSISSDEVNFLVYRYLQESGFSHSAFTFGIESHISQSNINGALVPPAALISIIQKGLQYVEA  
EVSINEDGTLFDGRPIESLSLIDAVMPDVVQTRQQAYRDKLAQQQAAAAAAAAAASQQ  
GSAKNGENTANGEENGAHTIANNHTDMMEVDGDVEIPPNAKAVVLRGHESEVFICAWNP  
VSDLLASGSGDSTARIWNLSNSTSGSTQLVLRHCIREGGQDVPSNKDVTSLDWNSEG  
TLLATGSYDGFARIWTKDGNLASTLGQHKGPFAKWNKKGNFELSAGVDKTTIWDHT  
GEAKQQFPFHSAPALDVDWQSNNTFASCSTDMCIHVCKLGQDRPIKTFQGHTNEVNAI  
KWDPTGNLLASCSDMTLKIWSMKQDNCVHDLQAHNKEIYTIKWSPTGPGTNNPNANL  
MLASASFDSTVRLWDVDRGICHTLTKHQEPVYSVAFSPDGRYLASGSFSDKCVHIWNTQ  
TGALVHSYRGTTGGIFEVCWNAAGDKVGASASDGSVCVLDLRK

SEQ ID No:247

MDEKVFTKELDQWIEQLNECKQLSESQVKSCEKAKEILTKESNVQEVRCPVTVCGDV  
HGQFHDLMELFRIGGKSPDTNYLFMGDYVDRGYYSVETVTLVALKVRYRERITILRGN  
HESRQITQVYGFYDECLRKYGNNANVWKYFTDLFDYLPLTALVDGQIFCLHGGLSPSIDTL  
DHIRALDRLQVEPHEGPMCDLLWSDPDDRGGWGISPRGAGYTFGQDISETFNHANG  
TLVSRHQLVMEGYNWCHDRNVVTIFSAPNYCYRCGNQAAIMELDDTLKYSFLQFDPA  
PRRGEPHVTRRTPDYFL

SEQ ID No:248

MDDKAFTKELDQWVEQLNECKQLNENQVRTLCEKAKEILTKESNVQEVRCPVTVCGDV  
HGQFHDLMELFRIGGKSPDTNYLFMGDYVDRGYYSVETVTLVALKVRYPERITILRGN  
HESRQITQVYGFYDECLRKYGNNANVWKYFTDLFDYLPLTALVDGQIFCLHGGLSPSIDTL  
DHIRALDRLQVEPHEGPMCDLLWSDPDDRGGWGISPRGAGYTFGQDISETFNHANG  
TLVSRHQLVMEGYNWCHDRNVVTIFSAPNYCYRCGNQAAIMELDDTLKYSFLQFDPA  
PRRGEPHVTRRTPDYFL

SEQ ID No:249

AAADGDDSLYPIAVLIDELRNEDVQLRLNSIKKLSTIALALGVERTRSELLPFLTDITYDED  
EVLALAEQLGTFTTLVGGPEYVHCLLPPLSLATVEETVVRDKAVESLRAISHEHSPSD  
LEAHFVPLVKRLAGGDWFTSRTSACGLFSVCYPRVSSAVKAELRQYFRNLCSDDTPMV

RRAAASKLGEFAKVLELDNVKSEIIPMFSNLASDEQDSVRLlaveacvnIAQLLPQEDLE  
 ALVMPTLRQAAEDKSWAVRYMVADKFTELQKAVGPEITKTDLVPAFQNLMDCEAEVR  
 AAASHKVKEFCENLSADCRENVMSQILPCIKELVSDANQHVKSALASVIMGLSPILGKD  
 NTIEHLLPLFLAQLKDECPEVRLNIISNLDVCVNEVIGIRQLSQSLLPAIVELAEDAKWRVRL  
 AIIEYMPLLAGQLGVEFFDEKLSLCMAWLVDHVYAIREAATSNLKKLVEKFGKEWAHA  
 TIIPKVLAMSGDPNYLHRMTTLFCINVLSVCGQDITTKHMLPTVLRMAGDPVANVRFNV  
 AKSLQKIGPILDNSTLQSEVKPILEKLTQDQDQDVVKYFAQEALTVLSLA

SEQ ID No:250

MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQTPTEDGS  
 EEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAAEEAGIGDTPSLÉ  
 DEAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPQKGQANATRIP  
 AKTPPAPKTPPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVR  
 TPPKSPSSAKSRLQTAPVPMPLKKNVSKSIGSTENLKHQPGGGKVQIINKKLDLSNVQS  
 KCGSKDNIKHVPGGGSVQIVYKPVDLISKVTSKCGSLGNIHHKPGGGQVEVKSEKLDLK  
 DRVQSKIGSLDNITHVPGGGNKKIETHKLTFRENAKAKTDHGAEIVYKSPVVSQDTSR  
 HLSNVSSSTGSIDMVDSPQLATLADEVSAASLAKQGL

SEQ ID No:251

GLTISSLFSRLFGKKQMRILMVGLDAAGKTTILYKLLGEIVTTIPTIGFNVETVEYKNICFT  
 VWDVGGQDRIRPLWKHYFQNTQGLIFVVDSDNRERIQEVADELQKMLLVDELRDVLL  
 LFANKQDLPNAMAISEMTDKLGLQSLRNRTWYVQATCATQGTGLYEGLDWLSNELSKR

SEQ ID No:252

EDSLLKDLFQDYERWVRPVEHLNDKIKIKFGLAISQLVDVDEKNQLMTTNVWLKQEWID  
 VKLRWNPDDYGGIKVIRVPSDSVWTPDIVLFDNAVGDQVDDKTKALLKYTGEVTWIPP  
 AIFKSSCKIDVTYFPFDYQNCTMKFGSWSYDKAKIDLVLIGSSMNLKDYWESGEWAIKA  
 PGYKHDIKYNCCIEIYPDITYSLYIRRLPLFYTNLIIPCLLISFLTVLVLFYLPSCDCGEKVTLCI  
 SVLLSLTVFLLVITETIPSTSLVIPLIGEYLLFTMIFVTLISIVITVFLNVHYRTPTTHTMPSW  
 VKTVFLNLLPRVMFMTRPTSNEGNAQKPRPLYGAELSNLNCFSRAESKGCKEGYPCQD  
 GISCHPPPSMCLSSASTSCSPWCWSPSPSSPASVCSMCTTARPAPTPWHPGSSAASC  
 TSCLPSSSKRPGPDSSPARAFPPSKSCVTKEATATSTSPSNFYGNSMYFVNPASAAS  
 KSPAGSTPVAIPRDFWLRSSGRFRQDVQEALGVSFIAQHMKNDDEDQSVVEDWKYV  
 AMVVDRLFLWVFMFVCLVGLTVGLFLPP

SEQ ID No:253

MVWPWVAMASRWGPLIGLAPCCLWLLGAVLLMDASARPANHSSTRERVANREENEIL  
PPDHLNGVKLEMDGHLNRGFHQEVFLGKDLGGFDEDAEPRRSRRKLMVIFSKVDVNT  
DRKISAKEMQRWIMEKTAEHFQEAMEESKTHFRAVDPDGDGHVSWDEYKVKFLASKG  
HSEKEVADAIRLNEELKVDEETQEVLLENLKDRWYQADSPPADLLLTEEEFLSFLHPEHS  
RGMLRFMVKEIVRDLDQDGDQKQLSVPEFISLPVGTVENQQGQDIDDNWWVKDRKKEFEE  
LIDSNHDGIVTAAEELESYMDPMNEYNALNEAKQMIAVADENQNHLEPEEVLKYSEFFT  
GSKLVDYARSVHEEF

SEQ ID No:254

MVAPGSVTSRLGSVFPFLLVLVDLQYEGAECGVNADVEKHLELGKKLLAAGQLADALS  
QFHAAVDGDPDNYIAYYRRATVFLAMGKSKAALPDLTKVIQLKMDFTAARLQRGHLLLK  
QGKLDEAEDDFKKVLKSNPSENEEKEAQSQLIKSDEMQRRLRSQALNAFGSGDYTAAIAF  
LDKILEVCVWDAELRELRAECFIKEGEPRKAISDLKAASKLKNNDTEAFYKISTLYYQLGD  
HELSEVRECLKLDQDHKRCFAHYKQVKLNKLIESAEELIRDGRYTDATSKYESVMK  
TEPSIAEYTVRSKERICHCFKDEKPVEAIRVCSEVLQMEPDNVNALKDRAEAYLIEEMY  
DEAIQDYETAQEHNENDQQIREGLEKAQRLLKQSQKRDYYKILGVKRNAKKQEIIKAYRK  
LALQWHPDNFQNEEEKKKAEEKFIDIAAAKEVLSDPEDMRKKFDDGEDPLDAESQQGGG  
GNPFHRSWNSWQGFNPFSSGGPFRRKFHFN

SEQ ID No:255

MERSPGEGSPSPMDQPSAPSDPTDQPPAAHAKPDPGSGGQPAGPGAAGEALAVLT  
SFGRRLVLIPVYLAGAVGLSVGFVLFGLALYLGWRRVRDEKERSLRAARQLLDDEEQL  
TAKTLYMSHRELPAWVSFPDVEKAEWLNKIVAQVWPFLGQYMEKLLAETVAPAVRGSN  
PHLQTFTRVELGEKPLRIIGVKVHPGQRKEQILLDNISYVGDVQIDVEVKKYFCKAGV  
KGMQLHGVLRVILEPLIGDLPFVGAVSMFFIRRPDLINWTGMTNLLDIPGLSSLSDTMIM  
DSIAAFLVLPNRLLVPLVPDLQDVAQLRSPLPRGIIRIHLLAARGLSSKDKYVKGLIEGKSD  
PYALVRLGTQTFCSRVIDEELNPQWGETYEV MVHEVPGQEIEVEVFDKDPDKDDFLGR  
MKLDVGKVLQASVLDDWFPLQGGQGQVHLRLEWLSLLSDAEKLEQVLQWNWGVSSR  
PDPPSAAILVVYLDRAQDLPLKKGNKEPNPMVQLSIQDVTQESKAVYSTNCPVWEEAFR  
FFLQDPQSQELDVQVKDDSRALTGLALTPLARLLTAPELILDQWFQLSSSGPNRSRLYM  
KLVMRILYDSSEICFPTVPGCPGAWDVDSNPQRGSSVDAPPRPCHTTPDSQFGTEH  
VLRHVLEAQDLIAKDRFLGGLVKGKSDPYVKLKLAGRSFRSHVVREDLNPRWNEVFEVI

VTSPGQEEVEVFDKDLKDDFLGRCKVRLTTVLNSGFLDEWLTLEDVPSGRHLRLRLE  
RLTPRPTAAEEVLQVNSLIQTQKSAELAAALLSIYMERAE DLPLRKGTKHLSPYATLTV  
GDSSHKT KTISQTSAPVWDESASFLIRKPHTESLELQVRGEGTGVLGSLSLPLSELLVAD  
QLCLDRWFTLSSGQGQVLLRAQLGILVSQHSGVEAHSHSYSHSSSSSLSEEPELSGGPP  
HITSSAPELRQRLTHVDSPLEAPAGPLGQVKLT LWYYSEERKLVSI VHGCRLRQNGRD  
PPDPYVSLLLLPDKNRGTRKRTSQQKRTLSPEFNERFEWELPLDEAQRRLDVSVKSN  
SSFMSRERELLGKVQLDLAETDLSQGVARWYDLMDNKKDKGSS

SEQ ID No:256

MVVALRYVWPLLLCSPCLLIQIPEEYEGHHVMEPPVITEQSPRRLVVFPTDDISLKCEAS  
GKPEVQFRWTRDGVHFKPKEELGVTVYQSPHSGSFTITGNNSNFAQRFQGIYRCFASN  
KLG TAMSHEIRLMAEGAPKWPKETVKPVEVEEGESVVLPCNPPPSAEPLRIYWMNSKIL  
HIKQDERVTMGQNGNLYFANVLTSDNHSDYICAHFPGTRTIIQKEPIDLRVKATNSMID  
RKPRLLFPTNSSSHLVALQGQPLVLECIAEGFPTPTIKWLRPSGPM PADRVTYQNHNT  
LQLLKVGEEDDGEYRCLAENSLGSARHAYYVTV EAAPYWLHKPQSHLYGPGETARLDC  
QVQGRPQPEVTWRINGIPVEELAKDQKYRIQRGALILSNVQPSDTMVTQCEARNRHGL  
LLANAYIYVVLPAKILTADNQTYMAVQGSTAYLLCKAFGAPVPSVQWLDEDGTTVLQD  
ERFFPYANGTLGIRDLQANDTGRYFCLAANDQNNVTIMANLKV DATQITQGPRSTIEKK  
GSRVTFTCQASFDPSLQPSITWRGDGRDLQELGDS DKYFIEDGRLVIHSLDYS DQGN  
SCVASTELDVVESRAQLLVGSPGPVPRVLVSDLHLLTQSQVRVSWSPAEDHNAPIEKY  
DIEFEDKEMAPEKWYSLGKVPGNQTSTTLKLSPYVHYTFRVTAINKYGPGEPSPVSETV  
VTPEAAPEKNPVDVKGEGETTNM VITWKPLRWMDWNAPQVQYRVQWRPQGTRGP  
WQE QIVSDPFLVVSNTSTFVPYEIKVQAVNSQKG GPEPQVTIGYSGEDYPQAIPELEGIE  
ILNSSAVLVKWRPVDLAQVKGHLRGYNVTYWREGSQRKHSKRHHKDHVVVPANTTSV  
ILSGLRPYSSYHLEVQAFNGRGS GPASEFTFSTPEGVPGHPEALHLECQSNTSLLL RW  
QPPLSHNGVLTGYVLSYHPLDEGGKGQLSFNL RDPELRTHNLTDLSPHLR YRFQLQAT  
TKEGPGEAIVREGGTMALSGISDFGNISATAGENYSVVS WVPKEGQC NFRFHILFKALG  
EEKGGASLSPQYVSYNQSSYTQWDLQPD TDYEIHLFKERMFRHQMAVKTNGTGRVRL  
PPAGFATEGWFIGFVSAIILLLLVL LILCFIKRSKGGKYSVKDKEDTQVDSEARPMKDET F  
GEYRSLESDNEEKAFGSSQPSLNGDIKPLGSDDSLADYGGSDVDVQFNEDGSGFIGQYSG  
KKEKEAAGGNDSSGATSPINPAVALE

SEQ ID No:257

MAVRELCFPRQRQVLFVFLFWGVSLAGSGFGRYSVTEETEKGSFVWNLAKDLGLAEGE  
LAARGTRVVSDDNKQYLLLDSTGNLLTNEKLDREKLCGPKEPCMLYFQILMDDPFQIY  
RAELRVRDINDHAPVFQDKETVLKISENTAEGTAFRLERAQDPDGGGLNGIQNYTISPNSF  
FHINISGGDEGMIYPELVLDKALDREEQGELSLTLTALDGGSPSRSGTSTVRIVVLDVND  
NAPQFAQALYETQAPENSPIGFLIVKVAEDVDSGVNAEVSYSFFDASENIRTTTFQINPF  
SGEIFLRELLDYELVNSYKINIQAMDGGGLSARCRVLVEVLDNDNPPELIVSSFSNSVA  
ENSPETPLAVFKINDRDSGENGMVCYIQENLPFLKPSVENFYILITEGALDREIRAEYNI  
TITVTDLGTPLRKTEHNITVLVSDVNDNAPAFQTQTSYTLFVRENNSPALHIGSVSATDRD  
SGTNAQVTYSLLPPQDPLPLASLV SINADNGHLFALRSLDYEALQAFEFVRGATDRGS  
PALSREALVRVLVDANDNSPFVLYPLQNGSAPCTELVPRAAEPGYLVTKVVAVDGDS  
GQNAWLSYQLLKATEPGLFGVWAHNGEVRTARLLSERDAAKHRLVVLVKDNGEPPRS  
ATATLHLLLVDGFSQPYLPLPEAAPAQAAQAEADLLTVYLVVALASVSSLFLLSVLLFVAVR  
LCRRSRAASVGRCSVPEGPFGHLVDVARGAETLSQSYQYEVCLTGGPGTSEFKFLKPV  
ISDIQAQGPGRKGEENSTFRNSFGFNIQ

SEQ ID No:258

MEIRGALDLRKRQVLIFLVLLGLSRAGTESAHYSVAEETEIGSFVANLARDLGLGVEELS  
SREARVVSDDNKYLHLDLLTGNLLNEKLDRELCGSTEPCVLHFQVLENPLQFFRF  
ELCVKDINDHSPTFLDKEILIKISEGTTVGATFLMESAQDLVDGNSLQNYTISPNSHFYIK  
IPDSSDRKIYPELVLDRALDYEQEAELRLTLTAVDGGSPPKSGTTLVLIKVLNDINDNAPEF  
PQSLYEVQVPEDRPLGSIATISAKDL DAGNYGKISYTFHASEDIRKTFEINPISGEVNL  
RSPLD FEVIQSYTINIQTADGGGLSGKCTLLVKVMDINDNPPEVTISSITKRIPENASETLV  
ALFSILDQDSGDNGRMICSIQDNLPFFLKPTFKNFFTLVSEKALDRESQAEYNITITVTDL  
GTPRLKTEYNITVLLSDVNDNAPTFTQTSYTLFVRENNSPALHIGSVSATDRD SGTNAQV  
NYSLLPPQDRHLPLASLV SINADNGHLFALRSLDYEALQEFEFVRGATDRGSPALSSEA  
LVRVLVDANDNSPFVLYPLQNGSAPCTELVPRAAEPGYLVTKVVAVDGDSGQNAWLS  
YQLLKATEPGLFGVWAHNGEVRTARLLSERDAAKHRLVVLVKDNGEPPRSATATLHVL  
LVDGFSQPYLPLPEAAPAQAAQADSLTVYLVVALASVSSLFLFSVLLFVAVRLCRRSRAAS  
VGRCSVPEGPFGHLVDVSGTGTLSQSYQYEVCLTGGSGTNEFKFLKPIIPNFQVHDT  
GRNMGEIENFRNSFGLNIQ

SEQ ID No:259

MEARVERAVQKRQVLFVFLGMSWAGAEPLRYFVAEETERGTFLTNLAKDLGLGVGE  
LRARGTRIVSDQNMQILLSSLTGDLNLLNEKLDREELCGPREPCVLPFQLLLEKPFQIFRA

ELWVRDINDHAPVFLDREISLKILESTTPGAAFLLESAQDSDVGTNSLSNYTISPNAVYFHI  
 NVHDSGEGNIYPELVLNQVLDREEIPEFSLTLTALDGGSPPRSGTALVRILVLDVNDNAP  
 DFVRSLYKVQVPENSPVGSMMVSVSARDLDTGSNGEIAYAFSYATERILKTFQINPTSG  
 SLHLKAQLDYEAIQTYTLTIQAKDGGGLSGKCTVVVDVTDINDNRPELLSSLTSPIAENS  
 PETVVAVFRIRDRDSGNGKTVCSIQDDVPFILKPSVENFYTLVTEKPLDRERNTEYNITI  
 TVTDLGTPRLKTEHNITVLVSDVNDNAPAFQTQSYTLFVRENNSPALPIGSVSATDRDSG  
 TNAQVIYSLPSQDPHLPLASLV SINADNGHLFALRSLDYEALQAFEFVRVGATDRGSPAL  
 SSEALVRVLVLDANDNSPFVLYPLQNSSAPCTEPLPRAAEPGYLVTKVAVDGDGSGQN  
 AWLSYQLLKATEPGLFGVWAHNGEVRTARLLSERDAAKQRLVVLVKDNGEPPRSATAT  
 LHVLLVDGFSQPYRLPEAAPDQANSLTVYLVVALASVSSLFLLSVLLFVAVRLCRRSRA  
 APVGRCSVPEGPFRHLVDLSGTGTLQSQSYQYEVCLTGGSGTNEFKFLKPIIPNLLPQS  
 TGREVEENRPFQNNLGF

SEQ ID No:260

MRVRIGLTLLLCAVLLSLASASSDEEGSQDESLSKTTLTSDSVKDHTTAGRVVAGQIF  
 LDSEEESELESSIQEEEDSLKSQEGESVTEDISFLESPNPENKDYEPPKKVRKPALTAIEG  
 TAHGEPCHFPFLFLDKEYDECTSDGREDGRLWCATTYDYKADEKWGFCETEEEEAAKR  
 RQMQEAEEMMYQTGMKILNGSNKKSQKREAYRYLQKAASMNHTKALERVSYALLFGDY  
 LPQNIQAAREMFELTEEGSPKGQTALGFLYASGLGVNSSQAKALVYYTFGALGGNLIA  
 HMYLGYRYWAGIGVLQSCESALTHYRLVANHVASDISLTGGSVVQRIRLPDEVENPGM  
 NSGMLEEDLIQYYQFLAEKGDVQAQVGLGQLHLHGGRGVEQNHQRAFDYFNLAANAG  
 NSHAMAFLGKMYSEGSDIVPQSNETALHYFKKAADMGNPVGQSGLGMAVLYGRGVQV  
 NYDLALKYFQKAAEQGWVDGQLQLGSMYYNGIGVKRDYKQALKYFNLASQGGHILAFY  
 NLAQMHASGTGVMRSCHTAVELFKNVCERGRWSERLMTAYNSYKGDGDYNAAVIQYLL  
 LAEQGYEVAQSNAAFILDQREASIVGENETYPRALLHWNRAASQGYTVARIKLGDYHFY  
 GFGTDVDYETAFIHYRLASEQQHSAQAMFNLGYMHEKGLGIKQDIHLAKRFYDMAAEA  
 SPDAQVPVFLALCKLGVVYFLQYIRETNIRDMFTQLDMDQLLGPWDLYLMTIALLLGT  
 VIAYRQRQHQDMPAPRPPGPRPAPPQQEGPPEQQPPQ

SEQ ID No:261

MSTEKVDQKEEAGEKEVCGDQIKGPDKEEPPAAASHGQGWRPGGRAARNARPEPG  
 ARHPALPAMVNDPPVPALLWAQEVGQVLAGRARRLLLQFGVLFCTILLLLWVSVFLYGS  
 FYYSYMPVSHLSPVHFYRTDCDSSTTSLCSFPVANVSLTKGGRDRVLMYGQPYRVT  
 LELELPESPVNQDLGMFLVTISCYTRGGRIISTSSRSVMLHYRSDLLQMLDTLVFSSLLL

GFAEQKQLLEVEYADYRENSYVPTTGAIIEIHSKRIQLYGAYLRIHAHFTGLRYLLYNFP  
 MTCAFIGVASNFTFLSVIVLFSYMQWVWGGIWPRHRFSLQVNIRKRDNSRKEVQRRISA  
 HQPGAGPEGQEESTPQSDVTEDESGPEDPSGTEGQLSEEEKPDQQPLSGEEELEPEA  
 SDGSGSWEDAALLTEANLPAPAPASASAPVLETLGSSEPAGGALRQRPTCSSS

SEQ ID No:262

SRVLCWVQTPVRPGGFLVSQARASHSPAUVCGRPRPQRTRPPTLTCPLSCPSPIAP  
 SLPSRCPSPPHAASARLSPPRPPTRPLFSGNRSFRSARLESFWPDSAASFHRPSLLLPP  
 CGSVANIFKGLVILPEMSLVIRNLQRVIPRRAPLRSKIEIVRRILGVQKFDLGIICVDNKNIQ  
 HINRIYRDRNVPTDVLSFPFHEHLKAGEFPQPDFPDDYNLGDIFLGVEYIFHQCKENEDY  
 NDVLTVTATHGLCHLLGFTHTGTEAEWQQMFQKEKAVLDELGRRTGTRLQPLTRGLFG  
 GS

SEQ ID No:263

MQPAKEVTKASDGSLLGDLGHTPLSKKEGIKWQRPRLSRQALMRCCLVKWILSSTAPQ  
 GSDSSDSELELSTVRHQPEGLDQLQAQTKFTKKEQLQSLYRGFKNECPTGLVDEDTFKLI  
 YAQFFPQGDATTYAHFLFNAFDADGNGAIHFEDFVGLSILLRGTVHEKLKWAFLNYDIN  
 KDGYITKEEMLAIMKSIYDMMGRHTYPILREDAPAEHVERFFEKMDRNQDGVVTIEEFLE  
 ACQKDENIMSSMQLFENVI

SEQ ID No:264

MVQKSRNGGVYPGPSGEKKLVGVFVGLDPGAPDSTRDGALLIAGSEAPKRGSIKSKPR  
 AGGAGAGKPPKRNAFYRKLNFLYNVLERPRGWAFIYHAYVFLVFSCLVLSVFSTIKE  
 YEKSSSEGALYILEIVTIVVFGVEYFVRIWAAGCCCRYRGWRGRLKFARKPFCVIDIMVLI  
 SIAVLAAGSQGNVFATSALRSLRFLQILRMIRMDRRGGTWKLLGSSVYAHSKELVTAWY  
 IGFLCLILASFLVYLAEKGENDHFDYADALWWGLITLTTIGYGDKYPQTWNGRLLAATF  
 TLIGVSFFALPAGILGSGFALKVQEQHRQKHFEKRRNPAAGLIQSAWRFYATNLSRTDL  
 HSTWQYYERTVTVP MYSSQTQTYGASRLIPPLNQLELLRNLSKSKGLAFRKDPPPEPSP  
 SKGSPCRGPLCGCCPGRSSQKVSLKDRVFSSPRGVAAGKKGSPQAQTVRRSPSADQ  
 SLEDSPSKVPKSWSFGRDRARQAFRIKGAASRQNSEEASLPGEDIVDDKSCPCEFT  
 EDLTPGLKVSIRAVCVMRFLVSKRKFKESLRPYDVM DVIEQYSAGHLDMLSRIKSLQSR  
 VDQIVGRGPAITDKDRTKGPAEAEALPEDPSMMGR LGKVEKQVLSMEKKLDFLVNIYMQ  
 RMGIPPTETEAYFGAKEPEPAPPYHSPEDSREHVDRHGCIVKIVRSSSSTGQKNFSAPP  
 AAPPVQCPPSTSWQPQSHPRQGHGTSPVGDHGS LVRIPPPPAHERSL SAYGGGNRAS

MEFLRQEDTPGCRPPEGNLRSDTSISIPVDHEELERSFSGFSISQSKENLDALNSCY  
AAVAPCAKVRPYIAEGESDSDLCCTPCGPPPRSATGEGPFGDVGWAGPRK

SEQ ID No:265

MRLKIGFILRSLLVGSFLGLVVLWSSLTPRPDDPSPLSRMREDRDVNDPMPNRGGNG  
LAPGEDRFKPVPWPHVEGVEVDLESIRRINKAKNEQEHHAGGDSQKDIMQRQYLTFK  
PQTFTYHDPVLRPGILGNFEPKEPEPPGVVGGPGEKAKPLVLGPEFKQAIQASIKEFGF  
NMVASDMISLDRNVNDRQEECKYWHYDENLLTSSVVIVFHNEGWSTLMRTVHSVIRK  
TPRKYLAIEVLIDDFSNEHLKEKLDEYIKLWNGLVKVRNERREGLIQARSIGAQKAKLG  
QVLIYLDACEVAVNWAYPLVAPISKDRITCTVPLIDVINGNTYEIIPQGGGDEDGYARGA  
WDWSMLWKRVPLTPQEKRLRKTKEPYRSPAMAGGLCAIEREFFFELGLYDPSLQIWG  
GENFEISYKIWWQCGKLLFVPCSRVGHYRLEGWQGNPPPIYVGSSPTLKNYVRVVEV  
WWDEYKDYFYASRPESQALPYGDISELKKFREDHNCQSFKWFMEEIAYDITSHYPLPP  
KNVDWGEIRGFETAYCIDSMTNGGFFVELGPPCHRMGGNQLFRINEANQLMQYDQCL  
TKGADGSKVMITHCNLNEFKEWQYFKNLHRFTHIPSGKCLDRSEVLHQVFISNCDSSKT  
TQKWEMNNIHSV

SEQ ID No:266

MAQALPWLLLWMGAGVLPAGHTQHGIRLPLRSGLGAPLGLRLPRETDEEPEEPGRR  
GSFVEMVDNLRGKSGQGYVEMTVGSPQTLNVLDTGSSNFAVGAAPHPFLHRYQ  
RQLSSTYRDLRGVYPYTQGWEGELGTDLVSIHPGNVTVRANIAAITESDKFFINGS  
NWEIGILGLAYAEIARPDSDLVQTHVPNLFSLQLCGAGFPLNQSEVLASVGG  
SMIIGGIDHSlyTGSlyWYTPIRREWYVEIIVRVEINGQDLKMDCKEYNYDKSIVNSGTTN  
LRLPKKVFEAAVKSIAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVT  
NQSFRTILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRI  
GFAVSACHVHDEFRTAAVEGPFVTLDMEDCGYNIPQTDESTLMTIAYVMAAICALFMLP  
LCLMVCQW RCLRCLRQQHDDFADDISLLK

SEQ ID No:267

MGAAVFFGCTFVAFGPAFALFLITVAGDPLRVILVAGAFFWLVSLLASVWWFILVHVT  
RSDARLQYGLLIFGAAVSVLLQEVFRFAYYKLLKKADEGLASLSEDGRSPISIRQMAYVS  
GLSFGIISGVFSVINILADALGPGVVGIIHGDSPIYFLTSAFLTAAIILLHTFWGVVFFDACE  
RRRYWALGLVVGSHLLTSGLTFLNPWYEASLLPIYAVTVSMGLWAFITAGGSLRSIQRS  
LLCKD

PCT/EP2004/009771



25

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINE(S) OR MARK(S) ON ORIGINAL DOCUMENT**
- ☒ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER: \_\_\_\_\_**

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**